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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

July 10, 2001

Mr. Jaime Henriquez
Food and Drug Administration
Center for Drug Evaluation and Research
Advisors and Consultants Staff, HFD-21
5630 Fishers Lane
Rockville, Maryland 20857

Re: NDA 21-272
Remodulin™ (treprostinil sodium) Injection
Briefing Document for Cardiovascular and
Renal Drugs Advisory Committee

Dear Mr. Henriquez:

A New Drug Application seeking approval for Remodulin™ (treprostinil sodium) Injection for the treatment of Pulmonary Arterial Hypertension was submitted to the FDA's Division of Cardio-Renal Drug Products on October 16, 2000. The Division Director, Dr. Raymond Lipicky, advised United Therapeutics Corp. that this NDA will be considered by the Cardiovascular and Renal Drugs Advisory Committee on August 9, 2001.

We are providing herewith the enclosed briefing document for distribution to members of the advisory committee. Under separate cover, we are also providing a copy of the briefing document to Ms. Joan Standaert, Executive Secretary of the Advisory Committee.

All materials provided herein are fully disclosable under the Freedom of Information Act.

Additionally, the briefing document is also provided electronically on the accompanying compact disc. Please contact me should you have any questions.

Sincerely,

Dean Bunce
Director Regulatory Affairs

cc: Ms. Joan Standaert

United Therapeutics CORPORATION

NDA 21-272
Remodulin™ (treprostinil sodium) Injection

Briefing Document for the Cardiovascular and Renal Drugs Advisory Committee

9 August, 2001

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1 BACKGROUND AND RATIONALE

1.1 Overview of Pulmonary Hypertension

Pulmonary arterial hypertension is an uncommon disease with a devastating clinical course. It is characterized by progressive increases in pulmonary artery pressure and pulmonary vascular resistance, ultimately producing right ventricular failure and death.

Pulmonary arterial hypertension (PAH) is defined by the World Health Organization as an elevated pulmonary arterial pressure due to intrinsic pulmonary vascular disease.[1] PAH includes primary pulmonary hypertension (PPH) either sporadic or familial or PAH secondary to: collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, infection with human immunodeficiency virus, drugs, toxins or persistent pulmonary hypertension of the newborn.

Estimates of the incidence of PPH ranged from 1 to 2 cases per million people in the general population.[2,3] The recent increased use of anorexiants in the United States has been correlated with an increase in incidence of patients with PPH.[2] Since PAH has only been recently described, there are no detailed estimates available as to the exact prevalence of PAH, although a global approximation of 50,000 patients is not unreasonable.

PAH can present at any age, depending on the underlying disorder. Patients with PPH are generally between 20 and 40 years of age, while those patients presenting with pulmonary hypertension associated with sleep apnea are generally between 40 and 70 years old. PAH is not gender specific; PPH occurs predominantly in females, and gender distribution in other forms of PAH reflects the underlying disorder.

The major obstacles to establishing a clinical diagnosis early in the course of the disease are the non-specific nature of the symptoms and the subtlety of the signs of less advanced disease. There are no signs or symptoms diagnostic for PAH. Accordingly, additional testing is required to establish the diagnosis. Non-invasive tests such as roentgenograms, electrocardiograms (ECGs), echocardiograms and computed tomograms are helpful but not definitive in establishing the diagnosis. Invasive tests including angiography and cardiac catheterization are used to establish the diagnosis.

The principal diagnostic hemodynamic criteria for PAH are: (1) mean pulmonary artery pressure (PAPm) > 25mm Hg at rest or > 30 mm Hg on exercise, (2) pulmonary vascular resistance (PVR) $\geq$ 3 mmHg/L/m^2, and (3) mean pulmonary capillary wedge pressure (PCWPm) or left ventricular end-diastolic pressure < 15 mmHg.[4] These criteria, together with echocardiographic evidence of right ventricular hypertrophy or dilation, normal left ventricular function and absence of mitral stenosis, have been applied in the pivotal clinical trials for treprostinil for patient selection.

The clinical features of PAH are dominated by dyspnea, exacerbated with exercise, and symptoms of fatigue and weakness, chest pain with or without an exertional element, dizziness, syncope, orthopnea and hemoptysis are also well described. As the duration and severity of the condition increases, right ventricular dysfunction and ultimately heart failure will occur with consequent edema and other features of heart failure.[4,5] The physical signs in patients with PAH reflect the pulmonary hypertension and right ventricular hypertrophy, hypoxemia and right heart failure.

Data from the National Registry for Primary Pulmonary Hypertension in the United States indicates that survival was related to the patients New York Heart Association (NYHA) Classification at the time of entry into the registry. Median survival for NYHA functional Class I or II was 58.6 months compared with 31.5 months for functional Class III and only 6 months for Class IV patients.[6] Death is usually due to advanced right ventricular failure or to a thromboembolic event.[3]

1.2 Current Therapy for Pulmonary Arterial Hypertension

PAH is an incurable disease. The goal of therapy is to relieve symptoms and improve survival. Standard therapies are generally either unproven or have minimal clinical data to support their use. Current medical therapy includes oral vasodilating agents, such as calcium channel blockers, inotropic agents, such as digitalis, to improve right ventricular performance, and anticoagulants, such as warfarin, to reduce thrombotic lesions. Supplemental oxygen is frequently used in patents with severe PAH, especially in the presence of hypoxemia at rest or during exercise. Atrial septostomy as a bridge to heart-lung and single and double-lung transplantation may represent an alternative for selected patients with severe PAH, though the disease process appears to be unaffected by the procedure.

Epoprostenol, prostacyclin, is the only approved therapy for the treatment of patients with PAH, specifically PPH and PAH associated with scleroderma. Both indications are based on studies in patients who were NYHA functional Class III or IV that evaluated the effect of epoprostenol over 12 weeks duration; exercise capacity as assessed by an unencouraged 6-minute walk test was the primary endpoint for both studies. Continuous intravenous (i.v.) infusion of epoprostenol was shown to improve exercise capacity, cardiopulmonary hemodynamics, signs and symptoms of disease and quality of life in patients with PAH.[7,8] These findings were based on randomized, but open-label trials that were not placebo controlled.

The underlying mechanism(s) of action of the chronic effects of epoprostenol is unknown and is likely multifactorial. Nevertheless, the use of epoprostenol, or structural analogues of epoprostenol, as a treatment for PAH is supported by the demonstration of an imbalance of thromboxane, a potent pulmonary vasoconstricting agent, and prostacyclin in patients with PPH, and the demonstration of a reduction in prostacyclin synthase in the pulmonary arteries of patients with PPH.

Though epoprostenol is accepted as mainstream treatment for of severely ill NYHA Class III or IV patients, epoprostenol therapy has several critically important limitations. Epoprostenol has a very short elimination half-life of several minutes, is unstable at room temperature and neutral pH, and must be administered continuously through a permanently indwelling central intravenous catheter. The very short half-life leaves patients susceptible to life-threatening complications from brief interruptions in drug delivery, sudden reductions in dosage, loss of infusate potency or withdrawal of therapy. In such circumstances patients may develop symptoms associated with rebound pulmonary hypertension, and deaths have occurred as a result. In addition, the central intravenous line serves as a source both for thromboembolic events and sepsis, both of which occur in patients treated with epoprostenol and both of which have resulted in death; the infusion site is also subject to infection. Moreover, not all patients are capable of managing the sterile set-up, reconstitution, and administration of epoprostenol on an ongoing basis. Finally, long-term treatment with epoprostenol is frequently associated with peripheral pain syndrome (particularly of the limbs) that may require treatment with opiates.

1.3 Rationale for Development of Treprostinil

Treprostinil, a stable structural analogue of epoprostenol, was developed for continuous subcutaneous (s.c.) administration to treat patients with PAH. It possesses a similar hemodynamic profile but has a longer elimination half-life than epoprostenol. Both treprostinil and epoprostenol act directly on the pulmonary and systemic arterial vascular beds causing vasodilation. Treprostinil also inhibits platelet aggregation in a manner similar to epoprostenol and is thought to have similar cytoprotective activity.

Importantly, however, as compared with epoprostenol, treprostinil has some important advantages: it is chemically stable at room temperature and neutral pH and has longer plasma elimination half-life (approximately 3 hours when administered s.c.). The longer half-life and chemical stability of treprostinil permits treprostinil to be administered in clinical practice by continuous subcutaneous infusion rather than by continuous intravenous infusion, thereby avoiding the need for permanent central intravenous catheter and completely eliminating the risk of potentially life-threatening septicemia and/or thrombosis related to the central venous catheter. The longer half-life of treprostinil also decreases the risk of rapid deterioration or clinical rebound associated with temporary interruptions of the infusion. Finally, treprostinil does not require the reconstitution of the solution nor refrigeration allowing the use of a microinfusion device.

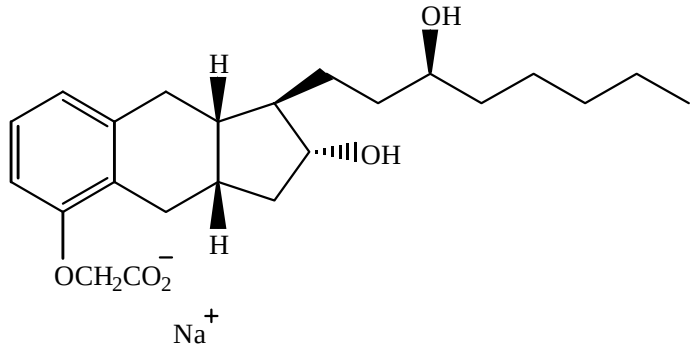
2 DEVELOPMENT OF TREPROSTINIL

2.1 Description of Treprostinil

Nonproprietary (generic) name: treprostinil sodium

Trade name: Remodulin™ Injection

Structural Formula



Molecular Formula

$C_{23}H_{33}NaO_5$

Molecular Weight

412.49

Remodulin Injection is formulated as a sterile solution packaged in multiple dose flint glass vials in concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/ml, and 10.0 mg/mL.

Remodulin is delivered via continuous subcutaneous infusion. Either MiniMed Model 506 or 407C pump (California, USA), originally designed for subcutaneous infusion of insulin, is used for the administration of Remodulin Injection. Remodulin Injection is dispensed from a polypropylene reservoir (i.e. a syringe without a needle) with a Teflon impregnated silicone O-ring. The drug is delivered at a programmed rate from the reservoir into the subcutaneous tissue by means of a PVC catheter with a High Density Polyethylene lining and a soft Teflon catheter tip (Sof-Set® Infusion Set). The MiniMed Inc. Drug Delivery System is distributed widely in the USA.

2.2 Preclinical Pharmacology and Toxicology

Pharmacology studies have demonstrated that treprostinil elicits concentration-dependent vasodilation and inhibition of ADP-induced platelet aggregation, as would be expected of a prostacyclin analogue. Treprostinil was somewhat less potent than epoprostenol, both as an antiaggregant and as a vasodilator.

The toxicology of treprostinil has also been extensively evaluated in a series of *in vitro* and *in vivo* genetic toxicology studies, reproductive toxicology studies in rats and rabbits, and single and repeated dose studies using the oral, intravenous and subcutaneous routes of administration. Continuous (up to 6 months) subcutaneous infusion in toxicokinetic studies also has been conducted in rats, dogs and rabbits. Toxicological findings were generally attributable to the pharmacological actions of treprostinil and were reversible. Treprostinil was not mutagenic or clastogenic in *in vitro* and *in vivo* genetic toxicology assays.

2.3 Summary of Clinical Development

This document summarizes the clinical experience from the administration of treprostinil to 843 patients or healthy volunteers in 15 clinical studies. Of these, 743 subjects with PAH were enrolled in 6 clinical studies, including both acute and chronic administration, in the treprostinil PAH development program (Table 2.3); the long-term safety database includes 631 patients with PAH. Pilot studies of acute administration of treprostinil in patients with congestive heart failure, critical limb ischemia, and portopulmonary hypertension have also been conducted but will not be summarized.

Table 2.3: Overview of All Clinical Studies

Protocol #	Study Design	Indication	Number of Subjects Treated	Dosage of Treprostinil	Treatment Duration
Clinical Pharmacology					
P01:01	Ac, OL	NYHA Class III/IV PPH comparison of epoprostenol to treprostinil	14	i.v. 5 ng/kg/min to MTD	Dose-escalation
P01:02	Ac, OL	NYHA Class III/IV dose escalation by cohort	25	i.v. 10 ng/kg/min s.c. 5, 10, 20 ng/kg/min	525 min
Pharmacokinetic Studies					
P01:07	Ac, OL Crossover	Bioavailability in Healthy Human Volunteers	15	i.v. 15 ng/kg/min s.c. 15 ng/kg/min	150 min each
P01:08	Ac, Crossover	Acetaminophen Interaction in Healthy Volunteers	29	s.c. 15 ng/kg/min	2 doses at 6 hr each
P01:09	C, OL	Chronic Pharmacokinetics in Healthy Volunteers	14	s.c. 2.5, 5, 10, 15 ng/kg/min	28 day

Protocol #	Study Design	Indication	Number of Subjects Treated	Dosage of Treprostinil	Treatment Duration
P01:10	Ac, OL	^{14}C Mass Balance in Healthy Volunteers	6	s.c. 15 ng/kg/min ^{14}C-treprostinol	8 hr
P01:12	single-blind, two-period, crossover, vehicle-controlled, repeat-dose	Warfarin interaction in Healthy Volunteers	16	s.c. 10 ng/kg/min	10 day
Controlled Clinical Studies *Randomized, Placebo-Controlled, Double-Blind Clinical Studies Supporting the Indication*					
UT P01:03 Pilot Study	C, R, DB, PC	NYHA Class III, IV PPH randomized (2:1) comparison of treprostinil plus conventional therapy to conventional therapy study	26	s.c. 2.5 to 40 ng/kg/min	8 wk
P01:04 North America Pivotal Study	C, R, DB, PC	NYHA Class II, III or IV PAH randomized comparison of treprostinil plus conventional therapy to conventional therapy study	224	s.c. 1.25 to 22.5 ng/kg/min	12 wk
P01:05 International Pivotal Study	C, R, DB, PC	NYHA Class II, III or IV PAH randomized comparison of treprostinil plus conventional therapy to conventional therapy study	246	s.c. 1.25 to 22.5 ng/kg/min	12 wk
Uncontrolled Clinical Studies *Ongoing Studies in PAH*					
P01:06	C, OL	PAH, evaluation of safety of treprostinil plus conventional therapy	631*****	s.c. 0.6 ng/kg/min to MTD	Chronic
P01:11	C, OL	PAH; epoprostenol to treprostinil transition	8 to date	s.c. transition from epoprostenol	Chronic
Clinical Study Reports of Uses Other Than Those Claimed in the Application					
BW P76:01	Ac, OL	NYHA Class III/IV CHF dose escalation	12	i.v. 5 ng/kg/min to MTD	Sequential dose-escalation
P02:01	Ac, OL	Mild/Moderate Portopulmonary hypertension	9	s.c. 10 ng/kg/min	450 min
P03:01	Ac, OL	Fontaine Stage III PVD/lower limb ischemia	8	i.v. 10 ng/kg/min to MTD	dose -escalation

Ac = acute, C = chronic, R = randomised, DB = double-blind, PC = placebo-controlled, OL = open- label
*****Includes 205 patients previously randomised to treprostinil in controlled studies P01:03, P01:04, P01:05; study ongoing (631 = number of patients included in last safety update to FDA)

2.4 Clinical Pharmacology and Pharmacokinetics

2.4.1 Pharmacodynamics

Study P01:01 was carried out to compare the acute hemodynamic effects of i.v. treprostinil and epoprostenol in Class III/IV patients with PPH. Fifteen patients were enrolled initially into an epoprostenol dose-ranging phase (epoprostenol was initiated at 2 ng/kg/min and increased every 15 min or longer to the maximum tolerated dose). Epoprostenol was discontinued during a 90 minute washout period followed by a treprostinil dose-ranging phase (treprostinil was initiated at 5 ng/kg/min and increased

every 30 min or longer to the maximal tolerated dose) followed by a 90 minute treprostinil maintenance phase and finally a 120 minute washout period.

Treprostinil and epoprostenol produced similar hemodynamic improvements (Table 2.4.1A); treprostinil's effects were maintained throughout 90 minutes of sustained i.v. administration. During the 120 minute washout period, the mean values for the hemodynamic parameters gradually returned to their baseline mean value. There was no apparent rebound effect.

Table 2.4.1A Key hemodynamic values at maximal tolerated dose of epoprostenol, treprostinil and end of treprostinil maintenance infusion, plus percent changes from baseline (Study P01:01).

Parameter	Mean ± SE (Percent change from baseline ± SE)		
	Epoprostenol MTD (n=14)	**Treprostinil MTD (n=14)**	**End of Treprostinil maintenance segment (n=10)**
HR (bpm)	89.9 ± 3.4 (+10.2 ± 3.3%)	87.2 ± 2.9 (+7.6 ± 2.3%)	79.3 ± 3.5 (-1.2 ± 5.0%)
RAP (mmHg)	9.9 ± 1.5 (-9.9 ± 6.4%)	9.2 ± 1.4 (-18.6 ± 6.2%)	6.9 ± 1.5 (-39.4 ± 10.6%)
CI (L/min/m^2)	3.2 ± 0.3 (+32.2 ± 9.0%)	3.4 ± 0.5 (+26.2 ± 11.7%)	3.2 ± 0.6 (+26.9 ± 16.7%)
PAPm (mmHg)	54.7 ± 5.2 (-1.6 ± 2.1%)	55.8 ± 6.3 (-0.6 ± 3.1%)	49.2 ± 5.1 (-8.9 ± 2.9%)
PVRI (mmHg/L/min/m^2)	14.5 ± 2.3 (-22.3 ± 5.0%)	15.4 ± 2.1 (-14.0 ± 6.6%)	13.2 ± 1.8 (-19.8 ± 8.7%)
SAPm (mmHg)	88.8 ± 3.1 (-5.4 ± 1.6%)	90.5 ± 2.9 (+2.6 ± 1.6%)	92.0 ± 3.8 (+1.1 ± 2.6%)
SVRI (mmHg/L/min/m^2)	26.3 ± 3.0 (-26.4 ± 4.9%)	28.6 ± 3.7 (-8.5 ± 7.6%)	29.6 ± 3.4 (-6.1 ± 10.0%)
SvO_2 (%)	na	na	69.2 ± 2.3 (+7.6 ± 5.1%)

MTD = maximal tolerated dose
na = not available

Study P01:02 was designed to compare the acute hemodynamic effects of i.v. and s.c. dosing with treprostinil in NYHA functional Class III/IV patients with PPH. Baseline hemodynamics were recorded, then all patients received a 75 minute i.v. infusion of treprostinil (10 ng/kg/min). Hemodynamic measurements were repeated at 15, 30, 60 and 75 minutes during the infusion. Following a 150 minute wash-out period, six patients were assigned to each of five s.c. dosage regimens of treprostinil: 5, 10, 20, 30, 40 ng/kg/min, and hemodynamic measurements were repeated at 15, 30, 60, 90, 120 and 150 minutes during s.c. administration of treprostinil. No patients were assigned to the two highest dosages after three patients experienced dose-limiting adverse events at 20 ng/kg/min treprostinil. Instead, seven additional patients were enrolled at the dosage level of 10 ng/kg/min.

Both the i.v. and s.c. treprostinil infusions of 10 ng/kg/min produced similar degrees of hemodynamic improvement (Table 2.4.1B).

Table 2.4.1B. Key hemodynamic values at end of infusions, plus percent changes from baseline to end of infusions for patients completing i.v. and s.c. treprostinil infusion (Study P01:02).

Parameter	MEAN ± SE AT END OF INFUSION (% change from baseline ± SE)	
	i.v. 10 ng/kg/min (n=24)	s.c. 10 ng/kg/min (n=12)
HR (bpm)	83.8 ± 2.4 (-0.6 ± 2.0%)	82.3 ± 2.9 (+0.2 ± 1.9%)
RAPm (mmHg)	8.8 ± 1.1 (+6.7 ± 13.4%)	8.3 ± 1.5 (-19.6 ± 13.3%)
Cl (L/min/m^2)	2.3 ± 0.1 (+12.1 ± 3.7%)	2.2 ± 0.2 (+19.4 ± 6.2%)
PAPm (mmHg)	59.9 ± 4.2 (-5.2 ± 2.3%)	58.8 ± 6.8 (-13.4 ± 3.5%)
PVRI (mmHg/L/min/m^2)	23.3 ± 3.8 (-17.1 ± 4.3%)	22.3 ± 4.7 (-26.3 ± 6.7%)
SAPm (mmHg)	89.5 ± 2.9 (-3.5 ± 1.5%)	85.5 ± 3.3 (-2.9 ± 2.5%)
SvO_2 (%)	63.3 ± 2.6 (+8.0 ± 4.0%)	56.8 ± 3.0 (+6.2 ± 2.5%)

2.4.2 Pharmacokinetics

In **Study P01:07**, 15 healthy volunteers received i.v. treprostinil, 15 ng/kg/min for 150 minutes followed by an identical dose of treprostinil given s.c. Following acute s.c. administration of 15 ng/kg/min treprostinil, the mean C_{max} was 1.47 ng/mL, the mean T_{max} was 2.51 hr and the *absolute bioavailability was 113.1%.* The AUC_{inf} may have been overestimated as a result of glucuronide conjugates of treprostinil being excreted in the bile and then being hydrolysed back to the parent drug and subsequently being reabsorbed. The mean apparent elimination half-life of treprostinil was 1.4 hr following acute s.c. administration compared to 0.9 hr following i.v. administration.

The steady-state plasma concentrations, plasma clearance, and elimination half-life were determined in 14 healthy volunteers (8 females, 6 males) who received increasing s.c. doses of 2.5, 5, 10 and 15 ng/kg/min of treprostinil over a 28 day period (**Study P01:09**). The mean steady-state plasma concentrations (0.259 ng/mL to 1.564 ng/mL) were dose proportional while the plasma clearance mean value (9.770 mL/kg/min to 10.445 mL/kg/min) remained consistent at the four dose levels. The *mean elimination half-life ($t_{½}$)* following the termination of chronic infusion in the final dosing period was *2.928 hr.*

2.4.3 Metabolism

Six healthy male volunteers were infused with [^{14}C] treprostinil (specific activity: 72.5 – 95.7 μCi) at a rate of 15 ng/kg/min for eight hours to characterize blood, plasma, urine, fecal radioactivity and to identify metabolites (**Study P01:10**). Twenty-four hours post-dosing, blood concentrations were below the limit of quantitation, but were still detectable in plasma. Urine was the main route of elimination; 75.6% of radioactivity was eliminated eight hours from the end of infusion. Total recovery within 24 hr of initiating the infusion, was 92.2% (urine 78.6%, feces including fecal wipes 13.6%). Five metabolites (64.4% of administered dose) were detected in the urine ranging from 10.2% to 15.5% of the administered dose. Three metabolites were the result of oxidation of the 3-hydroxyloctyl side chain, one was the product of glucuronidation of the parent drug and one was unidentified.

2.4.4 Drug Interactions

A study in 29 healthy adult volunteers (17 female, 12 male) has been completed (**Study P01:08**) evaluating the effect of multiple oral doses of acetaminophen on the pharmacokinetics and safety of s.c. treprostinil. Both acetaminophen and treprostinil undergo glucuronidation. In this interaction study, a randomized two-way crossover design was employed. There was no evidence of a pharmacokinetic interaction between acetaminophen and treprostinil.

Study P01:12 assessed the effects of continuous s.c. infusion of treprostinil 10 ng/kg/min on single dose warfarin (25 mg) pharmacodynamics and pharmacokinetics in 16 healthy volunteers. Each subject was randomised to receive nine days s.c. infusion with treprostinil or vehicle with warfarin being administered on the third day of each treatment period. Blood samples were collected up to 168 hr post-warfarin dosing to profile the pharmacokinetics of the R and S enantiomers of warfarin. The results of this study confirm the absence of any pharmacodynamic or pharmacokinetic interaction between warfarin and treprostinil.

The extent of protein binding of [^{14}C] treprostinil in female human plasma and the potential for protein binding interaction of treprostinil with digoxin and warfarin in female human plasma have been evaluated *in vitro*. Over the treprostinil concentration range of 0.33 to 10 μg/mL, [^{14}C] treprostinil was highly bound to human plasma proteins, with overall protein binding values of 91.0%. Treprostinil did not significantly affect the *in vitro* protein binding of [^{3}H] digoxin or [^{14}C] warfarin in pooled female human plasma.

A multivariate analysis was undertaken to investigate the relationship between various patient covariates and steady-state plasma clearance values of treprostinil in 186 patients with PAH in the two pivotal studies (**Studies P01:04 and P01:05**). The treprostinil infusion rate was kept constant during weeks 11 and 12, thus steady-state plasma concentrations of treprostinil were maintained throughout this period. The final model revealed obesity, concomitant furosemide and serum creatinine as determinants

of steady-state treprostinil plasma clearance. Furosemide and treprostinil undergo glucuronidation, therefore there may be an interaction resulting in a reduction in the plasma clearance of treprostinil. As <5% of s.c. administered Treprostinil is excreted unchanged in the urine and 98.9% of patients had serum creatinine values between 0.5 and 1.4 mg/dL, there is no clear explanation why serum creatinine is a predictor of treprostinil clearance. The sponsor believes that the package insert should include a caution statement on a potential interaction with furosemide (Appendix A)

An *in vitro* study demonstrated no inhibitory potential of treprostinil to human hepatic microsomal cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP 3A).

2.4.5 Summary of Clinical Pharmacology and Pharmacokinetics

In humans, following the initiation of subcutaneous infusion of treprostinil, steady-state plasma concentrations are usually achieved within 15 to 18 hours. Steady-state plasma concentrations of treprostinil are dose-proportional at subcutaneous infusion rates of 2.5 to 15 ng/kg/min; however, it is not known if the proportionality between dose and steady-state plasma levels is maintained at infusion rates greater than 15 ng/kg/min. Treprostinil when administered chronically as a subcutaneous infusion is completely absorbed and has a mean apparent elimination half-life of 3 hours compared to 45 minutes when administered intravenously. The mean volume of distribution and plasma clearance for treprostinil are 1.1 L/kg and 589 mL/kg/hr, respectively.

In clinical pharmacology studies, treprostinil was shown to be qualitatively similar in hemodynamic response and systemic adverse effects to i.v. epoprostenol, and quantitatively similar when both are given at maximum tolerated doses. Also, s.c. treprostinil is quantitatively similar to equal doses of i.v. treprostinil in hemodynamic effects; approximately 100% of the s.c. dose is bioavailable. No interaction with acetaminophen or warfarin was noted; furosemide contributed slightly (6%) to the plasma clearance of treprostinil based on multivariate modeling; treprostinil did not inhibit human P450 isoenzymes – thus there was little interaction with concomitant therapies for PAH.

3 MAJOR EFFICACY STUDIES WITH TREPROSTINIL

Three double-blind, placebo-controlled clinical trials have been carried out with treprostinil in patients with pulmonary arterial hypertension.

One controlled trial, Study P01:03, was a Phase II pilot trial in 26 patients with NYHA Class III/IV PPH, who were treated with placebo or treprostinil (1:2 ratio) for 8 weeks. In this study, treatment with subcutaneous treprostinil was well tolerated and was accompanied by a consistent (but not statistically significant) improvement in all efficacy measures. Patients who successfully completed the study 8 week assessments could enroll in an open, uncontrolled extended treatment study, P01:06.

Table 3 Summary of Efficacy Results for P01:03 (Change from Baseline)

Assessment	Treprostinil (n=17)	Placebo (n=9)	P-value
6 minute walk (median change)	+24 m	-6 m	0.500
Borg Dyspnea Score	0.00	+0.97	0.319
Dyspnea-Fatigue Rating	+0.57	-0.25	0.200
Hemodynamics			
CI (L/min/m^2)	+0.42	-0.03	0.065
PAPm (mm Hg)	0.0	-2.4	0.135
PVRI (mmHg/L/min/m^2)	-4.8	+0.2	0.065

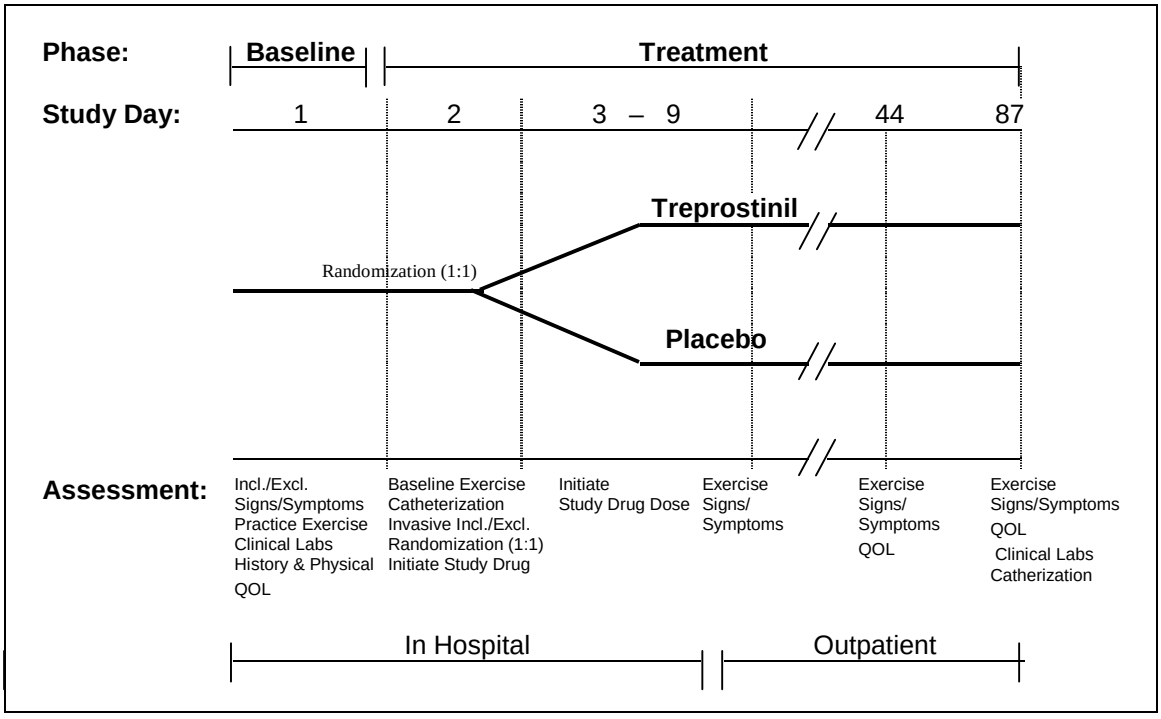
Based on the encouraging trends in this small study, two identical double-blind, placebo-controlled, randomized parallel-group studies (P01:04 and P01:05) were conducted. Studies P01:04 and P01:05 were designed to compare the efficacy and safety of chronic subcutaneous treprostinil plus conventional therapy versus placebo plus conventional therapy in symptom-limited (NYHA Class II, III or IV) patients with pulmonary arterial hypertension.

3.1 Design of Studies

In these two Phase III studies, patients ages 8 to 75 years with pulmonary arterial hypertension were screened for entry into the studies. Pulmonary arterial hypertension may have been due to no known causes (primary pulmonary hypertension) or may have been associated with a connective tissue disease or congenital systemic-to-pulmonary shunt. The diagnosis of pulmonary arterial hypertension was confirmed by prior cardiac catheterization or suspected based on previous data from medical history, physical examination, chest radiograph, electrocardiogram, echocardiogram, pulmonary function tests, pulmonary ventilation/perfusion scan, or pulmonary angiography. Candidates for study enrollment were to be optimally treated with conventional pulmonary hypertension therapy and stabilized prior to study entry; changes in concomitant PAH therapies were discouraged during the 12 week treatment period, unless clinically indicated.

Eligible patients were randomized in a 1:1 ratio (treprostinil: placebo) to 12 weeks of treatment with (1) conventional oral therapy plus continuous s.c. infusion of treprostinil or (2) conventional oral therapy plus continuous s.c. infusion of placebo. A central randomization scheme was used to assign patients to treatment groups. Randomization to active or placebo was stratified according to etiology of disease (primary versus secondary) and baseline exercise capacity (50-150 meters vs. 151 to 450 meters) and baseline vasodilator use (yes vs. no). No attempt was made to balance treatment within individual centers. Patients who successfully completed the study and completed the 12 weeks assessments could enroll in an open, uncontrolled extended treatment study, P01:06, along with those who completed study P01:03.

Figure 3.1 ***Overview of Study Design***



3.2 Measures of Efficacy

3.2.1 6-Minute Walk Distance

Exercise capacity was evaluated utilizing an unencouraged 6-minute walk test, which was assessed at baseline and Weeks 1, 6 and 12 following randomization. To reduce the effect of learning, a practice walk test was conducted up to 6 weeks prior to the baseline assessment. At each center, the walk test was conducted by a specific test administrator, who instructed each patient how to perform the test using a standardized script. Other than reminding the patient of the amount of time completed (2, 4 and

6 minutes), no other instruction or encouragement was offered. The test administrator was otherwise uninvolved in the study or care of the study patients; remained blinded to individual patient's treatment until the study was completed across all centers; and did not communicate the exercise test results to other study personnel involved in the trial. Immediately after completion of the 6-minute walk test, the magnitude of dyspnea was assessed by the patient using a 10-point scale (the Borg Dyspnea Score), which ranged from 0 (no dyspnea) to 10 (maximum dyspnea). In this manner, both the distance traversed and the symptoms experienced at the end of the walk test were measured. The exercise administrator recorded the initiation and completion times of the test, the distance walked, and the patient's estimate of their magnitude of shortness of breath at the end of the test (the Borg Score).

3.2.2 Symptoms and Signs of Pulmonary Hypertension

The assessment of symptoms and signs mimics precisely the usual interaction that occurs between patients and physicians during a routine office visit. In addition, such assessment allows for the evaluation of symptoms that occur spontaneously or at rest, including those that are not related to or evoked by exercise (and thus do not limit exercise tolerance).

A prespecified list of 8 symptoms and 8 physical signs characteristic of pulmonary hypertension were evaluated at baseline and Weeks 1, 6 and 12 after randomization. The symptoms were dyspnea, orthopnea, fatigue, chest pain, dizziness, syncope, palpitations and edema. According to the design of the case report form, investigators were not able to report symptoms that had improved but had not resolved. Similarly, the case report form was designed to detect symptoms that developed for the first time during the study but not symptoms that were originally present but had deteriorated. The physical signs were loud P2, right ventricular S3, right ventricular S4, right ventricular heave, murmur of tricupsid insufficiency, murmur of pulmonic insufficiency, hepatomegaly and jugular venous distention at 45 degrees. To ensure consistency, these were evaluated by the same physician for a given patient throughout the study.

3.2.3 Dyspnea-Fatigue Rating

An important clinical index used to measure general shortness of breath and the impact on the patient's lifestyle is the Dyspnea-Fatigue Rating. This clinical index of dyspnea and fatigue consists of three components, each rated on a scale of 0 to 4 (worst to best), for magnitude of the task that evokes dyspnea or fatigue, the magnitude of the pace (or effort) with which the task is performed and the associated functional impairment in general activities. The ratings for each component are collected and added to derive an aggregate score, which can range from 0, for the worst condition, to 12, for the best. The rating of each component provides a subjective assessment of their shortness of breath and the impact of the disease to their lifestyle. The Dyspnea-Fatigue Rating was assessed at baseline and 1, 6, 12 weeks following randomization.

3.2.4 Discontinuation due to Disease Progression, Transplantation or Death

Patients discontinuing from the study due to disease progression requiring rescue with epoprostenol or other i.v. agents, transplantation, or death were considered treatment failures.

3.2.5 Hemodynamic Variables

Hemodynamic variables were measured during right heart catheterization before and following 12 weeks of double-blind treatment. To avoid the possibility that knowledge of hemodynamic effects might influence the assessment of other efficacy variables, hemodynamic measurements were carried out after all other efficacy assessments. The following variables were measured directly: cardiac output, pulmonary arterial pressures, pulmonary capillary wedge pressure, mean right atrial pressure, systemic arterial pressures, heart rate and mixed venous oxygen saturation. The following variables were derived: cardiac index, stroke volume and index, pulmonary vascular resistance and index, systemic vascular resistance and index and total pulmonary resistance and index.

3.2.6 Quality of Life

Quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire, which provides insight into the patient's perspective of how a cardiovascular disorder affects their daily living. This assessment (which evaluates three dimensions: physical, emotional and global) was performed at baseline and after 6 and 12 weeks of double-blind treatment.

3.3 Prespecified Endpoints and Analyses

All analyses presented in this document were carried out based on the intention-to-treat principle and included all randomized patients, except one patient who was randomized to placebo and did not receive the study medication because of withdrawal of consent. In addition, data were censored at the time of inadvertent crossover for three patients who received incorrect study drug at their re-supply visit. The statistical analysis plan, which was submitted and agreed by the Division prior to unblinding, is attached as Appendix B.

3.3.1 Primary Endpoint

The primary endpoint of both study P01:04 and study P01:05 was the distance traversed during the 6-minute walk test. The significance of observed between-group differences in exercise distance was evaluated using a nonparametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test, adjusted for center, baseline exercise, vasodilator use at baseline and etiology (primary vs secondary pulmonary hypertension). The statistical plan specified that patients who failed to complete the trial

because of worsening of the underlying condition were given worst rank; those who failed to complete the study because of an adverse effect or for administrative reasons had their last double-blind rank carried forward.

Since P01:04 and P01:05 were identical in design and recruited similar patients, the sponsor proposed (before the blind of the studies was broken) that the studies be analyzed both individually and together utilizing a specified statistical approach, which minimized the risk of a false positive error. Accordingly, the trials would be considered positive if the P value for the combined analysis across both trials was < 0.05 and both trials individually achieved a $p < 0.05$ for the primary endpoint. The trials would also be considered positive if the combined analysis across both trials provided a $P < 0.01$ and at least one of the individual trials achieved a $P < 0.05$ for the primary endpoint. This statistical analysis plan was accepted by the Division before the database was locked and before the data from the trials were analyzed. Following unblinding of the data, the two studies yielded very similar results, indicating that the concept of pooling the data across the two trials was appropriate.

3.3.2 Principal Reinforcing Endpoints

Specific limitations of using the 6-minute walk as the primary endpoint of studies P01:04 and P01:05 were recognized by the sponsor and discussed with the FDA before the inception of the major trials with treprostinil. As a result, the trials not only measured the distance traversed during the 6-minute walk test but also quantified the symptoms experienced at the end of the test (using the Borg dyspnea score). Furthermore, both protocols not only defined a primary endpoint (6-minute walk test), but also took the unique step of defining three principal reinforcing endpoints in addition to several secondary efficacy endpoints.

The prespecified principal reinforcing endpoints in both trials were:

- Symptoms and signs of pulmonary hypertension

  To facilitate analysis of the data, the sponsor prespecified that information regarding the emergence or resolution of symptoms and signs were to be combined into a single score. Each symptom or sign was assigned a value of –1, 0 or +1, depending on whether the symptom or sign had emerged (-1) or resolved (+1). If the symptom or sign was present at both the start and end of the study (or was absent at both the start and end of the study), a value of 0 was assigned (even if the symptom or sign had improved or deteriorated). The values of the 16 symptoms and signs were summed to yield a composite score. The composite scores were compared between treatment groups using the Wilcoxon Rank Sum Test. Missing data were not imputed for this analysis.

- Dyspnea-fatigue rating

The ratings for each of the three components were collected and added to derive an aggregate score, which range from 0, for the worst condition, to 12, for the best. Changes from baseline were compared between treatment groups using the Wilcoxon Rank Sum Test. Missing data were not imputed for this analysis.

- Mortality, transplantation and discontinuation of the study drug due to clinical deterioration

Differences in proportions and odds ratios were used to describe treatment differences in event rates.

3.3.3 Secondary Endpoints

Secondary endpoints were hemodynamics and Borg Dyspnea Score. Quality of Life (QOL) was also evaluated during the studies but was not specified as a primary or secondary endpoint.

- Hemodynamics

Changes from baseline in hemodynamic parameters were compared between treatment groups using parametric analysis of covariance, adjusting for baseline value. Missing data were not imputed for these analyses.

- Borg Dyspnea score

Changes from baseline in the Borg dyspnea score were compared between treatment groups using the Wilcoxon Rank Sum Test. Missing data were not imputed for this analysis.

- Quality of life

Changes from baseline in the global score, physical dimension score, and emotional dimension score were compared between treatment groups using the Wilcoxon Rank Sum Test. Missing data were not imputed for this analysis.

3.4 Treprostinil Administration

The general strategy used for the administration of treprostinil was to initiate treatment at a fixed dose and then to progressively increase the dose to reduce signs and symptoms of pulmonary hypertension and yet avoid symptoms of excess treprostinil. Consequently, doses of study drug were increased if a patient's symptoms of pulmonary hypertension did not improve or if the patient's clinical condition deteriorated and the patient became

increasingly symptomatic. Doses were not increased (and may have been decreased) if any changes in vital signs or clinical signs or persistent symptoms of excess drug were observed including any adverse event judged related to study drug (e.g., headache, nausea, emesis, restlessness, anxiety). The onset of significant pain, or worsening of pain, at the injection site was also reason for not increasing the dose of study drug and, if clinically necessary, a sufficient reason to reduce dose. If a patient's clinical condition deteriorated despite increased doses of study drug, and, if in the judgment of the investigator the patient's condition warranted 'rescue' treatment with intravenous prostaglandins or chronic intravenous inotropic agents, the study drug was permanently discontinued.

The initial dose of study drug in P01:04 and P01:05 was 1.25 ng/kg/min. If the initial dose of 1.25 ng/kg/min was not tolerated by the patient, this initial infusion rate was reduced. If the initial rate was tolerated, the infusion rate was increased as needed at increments not greater than 1.25 ng/kg/min per week for the first four weeks and then not greater than 2.5 ng/kg/min per week for the duration of the infusion. This strategy permitted the opportunity to observe individual patient sensitivity to study drug by slowing increasing dose during the initiation of therapy, but once assessed, it permitted doses to be increased more aggressively during the later half of study.

3.5 Study Conduct

3.5.1 Baseline Characteristics

A total of 470 patients were randomized into studies P01:04 and P01:05. In study P01:04, 224 patients were enrolled (111 to placebo and 113 to treprostinil). In study P01:05, 245 patients were enrolled (125 to placebo and 120 to treprostinil). The patients randomized to placebo and treprostinil were similar with respect to all baseline characteristics (Table 3.5.1).

Table 3.5.1 Baseline Characteristics of Studies P01:04 and P01:05

Baseline Characteristic	P01:04		P01:05	
	Treprostinil (N=113)	**Placebo (N=111)**	**Treprostinil (N=120)**	**Placebo (N=125)**
Age (years, mean ± SE)	45.3 ± 1.4	43.2 ± 1.4	43.9 ± 1.3	45.5 ± 1.3
Age group categories (N, [% total])				
8 to <16 years of age	6 (5.3)	4 (3.6)	3 (2.5)	1 (0.8)
16 to 64 years of age	96 (85.0)	100 (9.1)	107 (89.2)	111 (88.8)
>64 years of age	11 (9.7)	7 (6.3)	10 (8.3)	13 (10.4)
Gender (N, [% total])				
Females	96 (85)	95 (85.6)	101 (84.2)	90 (72.0)
Males	17 (15)	16 (14.4)	19 (15.8)	35 (28.0)
Race (N, [% total])				
Caucasian	91 (80.5)	86 (77.5)	107 (89.2)	112 (89.6)
Black	8 (7.1)	5 (4.5)	5 (4.2)	3 (2.4)
Asian	4 (3.5)	6 (5.4)	1 (0.8)	2 (1.6)
Hispanic	8 (7.1)	13 (11.7)	6 (5.0)	6 (4.8)
Native American	1 (0.9)	0 (0.0)	1 (0.8)	0 (0.0)
Other	1 (0.9)	1 (0.9)	0 (0.0)	2 (1.6)
PAH NYHA Classification (N, [% total])				
Class II	10 (8.8)	16 (14.4)	15 (12.5)	12 (9.6)
Class III	93 (82.3)	85 (76.6)	97 (80.8)	107 (85.6)
Class IV	10 (8.8)	10 (9.0)	8 (6.7)	6 (4.8)
PAH Diagnosis (N, [% total])				
PPH	61 (54.0)	59 (53.2)	73 (60.8)	77 (61.6)
PAH associated with:				
Scleroderma	8 (7.1)	6 (5.4)	4 (3.3)	7 (5.6)
Limited Scleroderma	9 (8.0)	5 (4.5)	4 (3.3)	2 (1.6)
Mixed Connective Tissue Disease	4 (3.5)	8 (7.2)	4 (3.3)	1 (0.8)
Systemic Lupus Erythematosus	4 (3.5)	10 (9.0)	3 (2.5)	8 (6.4)
Overlap Syndrome	0 (0.0)	1 (0.9)	1 (0.8)	1 (0.8)
Congenital systemic-to-pulmonary shunts	27 (23.9)	22 (19.8)	31 (25.8)	29 (23.2)
Six-minute Walk Test (m)				
Mean ± SE	326.6 ± 7.8	335.9 ± 8.1	326 ± 7.8	318.5 ± 7.9
Median (25^{th}-75^{th} percentile)	341.4 (263.7-390.0)	349.0 (272-407)	348.5 (268.5-396)	338.0 (272.0-377.0)
Most common PAH Signs & Symptoms (N, [% total])				
Dyspnea	113 (100)	109 (98.2)	120 (100)	125 (100)
loud P2 sound	109 (96.5)	109 (98.2)	111 (92.5)	117 (93.6)
Fatigue	106 (93.8)	97 (87.4)	105 (87.5)	107 (85.6)
Right ventricular heave	79 (69.9)	83 (74.8)	53 (44.2)	63 (50.4)
Dyspnea-Fatigue Rating (mean ± SE)	4.27 ± 0.19	4.71 ± 0.19	4.23 ± 0.17	4.17 ± 0.18
Borg Dyspnea Score	4.42 ± 0.2	4.34 ± 0.23	4.22 ± 0.23	4.44 ± 0.24
Quality of life				
Global	54.9 ± 2.55	56.5 ± 2.62	52.7 ± 2.04	53.4 ± 1.99
Physical	25.5 ± 1.06	25.6 ± 1.13	24.4 ± 0.83	25.2 ± 0.86
Emotional	12.8 ± 0.90	13.5 ± 0.82	11.6 ± 0.70	11.4 ± 0.65
Hemodynamics (mean ± SE)				
CI ($L/min/m^2$)	2.25 ± 0.08	2.25 ± 0.06	2.47 ± 0.08	2.23 ± 0.07
PVRI ($mmHg/L/min/m^2$)	27.28 ± 1.49	26.23 ± 1.53	25.79 ± 1.26	24.11 ± 0.91
PAPm (mmHg)	61.1 ± 1.60	60.7 ± 1.49	62.5 ± 1.67	59.2 ± 1.25
SvO_2 (%)	60.4 ± 0.96	60.7 ± 1.15	62.5 ± 1.0	59.8 ± 1.03
RAP_m(mmHg)	11.1 ± 0.5	10.3 ± 0.59	9.5 ± 0 .55	9.6 ± 051
Chemistry (mean±SE)				
Albumin (g/dL)	3.9 ± 0.04	4.0 ± 0.04	4.0 ± 0.04	4.0 ± 0.04
LDH (U/L)	246.9 ± 6.28	243.3 ± 6.93	249.8 ± 7.34	247.5 ± 7.09
Alkaline Phosphatase (U/L)	93.8 ± 3.77	89.8 ± 4.94	100.3 ± 7.12	91.68 ± 3.66
BUN (mg/dL)	17.8 ± 0.88	15.8 ± 0.76	16.5 ± 0.59	17.0 ± 0.78
Creatinine (mg/dL)	0.9 ± 0.03	0.9 ± 0.02	0.9 ± 0.02	0.9 ± 0.02
Sodium (mEq/L)	139.0 ± 0.325	139.4 ± 0.30	140.2 ± 0.34	139.94 ± 0.38
Potassium (mEq/L)	4.1 ± 0.06	4.2 ± 0.04	4.1 ± 0.05	4.2 ± 0.05
Hematology (mean±SE)				
Hemoglobin (d/L)	14.82 ± 0.19	14.89 ± 0.2	15.37 ±0.21	15.39 ± 0.21
Platelet Count (10^3/uL)	204.99 ± 6.78	204.77 ± 6.95	206.15 ± 7.24	215.33 ± 7.0
Neutrophils (%)	66.15 ± 1.04	64.16 ± 1.24	64.12 ± 0.9	64.36 ± 1.02
Hematocrit (%)	45.71 ± 0.68	46.02 ± 0.64	47.65 ± 0.74	46.9 ± 0.66

Urinalysis (Protein)				
None, Negative or Missing	82 (72.6)	6 (5.5)	81 (67.5)	70 (55.6)
Trace	10 (8.8)	12 (10.9)	13 (10.7)	16 (13.0)
1^+	10 (8.8)	12 (10.9)	7 (5.7)	18 (14.6)
2^+	4 (3.5)	8 (7.3)	13 (10.7)	14 (11.4)
3^+	8 (7.0)	3 (2.7)	8 (6.6)	5 (4.1)
Coagulation Time (mean±SE)				
Prothrombin Value (sec.)	14.1 ± 0.23	14.4 ± 0.29	18.6 ± 1.07	19.3 ± 0.92
INR	1.3 ± 0.03	1.3 ± 0.03	1.8 ± 0.1	1.7 ± 0.08
ECG Results				
Unknown	2 (1.8)	3 (2.7)	4 (3.3)	3 (2.4)
Normal	0 (0.0)	6 (5.5)	2 (1.6)	2 (1.6)
Abnormal	112 (98.2)	101 (91.8)	116 (95.1)	118 (95.9)
Vital Signs (mean±SE)				
Weight (kg)	73.3 ± 1.98	73.8 ± 1.9	67.6 ± 1.63	72.1 ± 1.47
Respiration Rate (breaths/min)	19.2 ± 0.27	19.5 ± 0.31	18.9 ± 0.36	19.1 ± 0.32
Pulse rate (bpm)	83.5 ± 1.17	82.4 ± 1.2	82.1 ± 1.05	81.8 ± 1.14
Blood pressure, systolic, at rest (mmHg)	116.7 ± 1.30	117.3 ± 1.61	115.5 ± 1.28	116.3 ± 1.48
Blood pressure, diastolic, at rest (mmHg)	73.3 ± 1.12	75.9 ± 1.06	73.4 ± 1.04	74.3 ± 0.95
PAH Concomitant Medications (Number (%) of Patients)				
Vasodilators	57 (50.4)	62 (55.9)	55 (45.8)	57 (45.6)
Calcium channel blockers	49 (43.4)	50 (45.0)	48 (40.0)	48 (38.4)
Other vasodilators	18 (15.9)	19 (17.1)	15 (12.5)	16 (12.8)
Steroids	9 (8.0)	7 (6.3)	3 (2.5)	5 (4.0)
Diuretics	69 (54.0)	54 (48.6)	67 (55.8)	75 (60)
Anticoagulants	61 (54.0)	58(52.3)	88 (73.3)	102 (81.6)
Digoxin	34 (30.1)	30 (27.0)	22 (18.3)	29 (23.2)
Oxygen	42 (37.2)	41 (36.9)	41 (34.2)	41 (35.2)
Analgesic	1 (0.9)	2 (1.8)	1 (0.8)	0 (0.0)
Any Concomitant PAHs	106 (93.8)	104 (93.7)	113 (94.2)	122 (97.6)

3.5.2 Patient Disposition

Of the 470 patients who were randomized and received study drug, 48 did not complete 12 weeks of double-blind treatment, 15 in the placebo group and 33 in the treprostinil group (Table 3.5.2). The reasons for early discontinuation in the placebo group were death (n=7), transplant (n=1), clinical deterioration requiring rescue therapy (n=6), an adverse experience (n=1) and withdrawn consent (n=1). The reasons for early discontinuation in the treprostinil group were death (n=7), clinical deterioration requiring rescue therapy (n=6), an adverse experience (n=18) and withdrawn consent (n=2).

Table 3.5.2 Summary of Patient Disposition

Disposition	**Number of Patients (%)**	
	Treprostinil	**Placebo**
Randomized to Study (Pooled 04/05)	**233**	**237**
Study 01:04	113	111
Study 01:05	120	126
Received Study Drug (Pooled 04/05)	**233 (100)**	**236 (99.6)**
Study 01:04	113 (100)	111 (100)
Study 01:05	120 (100)	125 (99.2)

Received study drug for entire 12 weeks:		
(Pooled 04/05)	**200 (85.8)**	**221 (93.2)**
Study 01:04	96 (85.0)	104 (93.7)
Study 01:05	104 (86.7)	117 (92.9)
Received study drug up to time of death:		
(Pooled 04/05)	**7 (3.0)**	**7 (3.0)**
Study 01:04	4 (3.5)	4 (3.6)
Study 01:05	3 (2.5)	3 (2.4)
Received study drug up to time of transplant:		
(Pooled 04/05)	**0 (0.0)**	**1 (0.4)**
Study 01:04	0 (0.0)	1 (0.9)
Study 01:05	0 (0.0)	0 (0.0)
Received study drug up to the time of clinical deterioration requiring rescue therapy:		
(Pooled 04/05)	**6 (2.6)**	**6 (2.5)**
Study 01:04	1 (0.9)	2 (1.8)
Study 01:05	5 (4.2)	4 (3.2)
Discontinued Due to AE		
(Pooled 04/05)	**18 (7.7)**	**1 (0.4)**
Study 01:04	12 (10.6)	0 (0.0)
Study 01:05	6 (2.5)	1 (0.8)
Withdrew Consent		
(Pooled 04/05)	**2 (0.9)**	**1 (0.4)**
Study 01:04	0 (0.0)	0 (0.0)
Study 01:05	2 (1.7)	1 (0.8)

3.5.3 Use of Treprostinil

The mean doses of study drug achieved at the end of the first week of therapy, at the mid-point and at the conclusion of each study is summarized in Table 3.5.3. As is seen with other prostaglandin analogs used to treat pulmonary arterial hypertension, drug infusion rates tend to increase over time.

Table 3.5.3 Summary of Study Drug Infusion Record

Study Evaluation Timepoint	**Mean Dose ± SE (ng/kg/min) (N)** Pooled 04/05[a] Study 04 Study 05	
	Treprostinil	**Placebo**
Initiation of dosing	**1.2 ± 0.01 (236)** 1.2 ± 0.01 (114) 1.2 ± 0.01 (122)	**1.2 ± 0.01 (233)** 1.2 ± 0.02 (110) 1.2 ± 0.01 (123)
End of Week 1	**2.0 ± 0.04 (233)** 1.9 ± 0.06 (113) 2.1 ± 0.05 (120)	**2.3 ± 0.04 (231)** 2.2 ± 0.05 (108) 2.3 ± 0.06 (123)
End of Week 6	**5.9 ± 0.21 (215)** 5.5 ± 0.28 (105) 6.2 ± 0.30 (110)	**10.0 ± 0.21 (223)** 9.2 ± 0.29 (106) 10.8 ± 0.28 (117)
End of Week 12	**9.3 ± 0.38 (202)** 8.9 ± 0.49 (96) 9.6 ± 0.56 (106)	**19.1 ± 0.33 (217)** 17.4 ± 0.55 (103) 20.5 ± 0.32 (114)
[a]Patients not receiving drug at the time of evaluation were included		

3.6 Efficacy Results

3.6.1 Primary Endpoint -- Exercise Capacity

When both study P01:04 and P01:05 are considered together, the distance walked during the 6-minute walk test increased by 10 meters in the treprostinil group but did not change in the placebo group. The Hodges-Lehman estimate for the between-group treatment effect was 16 meters (P = 0.0064). The results of the individual studies were consistent with each other and were consistent with the pooled analysis (P = 0.0607 for P01:04; P = 0.0550 for study P01:05), Table 3.6.1A.

Table 3.6.1A Change from Baseline in 6-Minute Walk Test at Week 12: Pooled and Individual Studies

Analysis Population Treatment Group	Median Change (m)	Median Difference[a] (m)	p-value
Pooled 04/05			
Treprostinil (N=232)	10.0	**16.0**	0.0064
Placebo (N=236)	0.0		
Study P01:04			
Treprostinil (N=113)	3.0	**13.0**	0.0607
Placebo (N=111)	1.0		
Study P01:05			
Treprostinil (N=119)	16.0	**18.5**	0.0550
Placebo (N=125)	-3.0		

[a] Hodges-Lehman Estimate

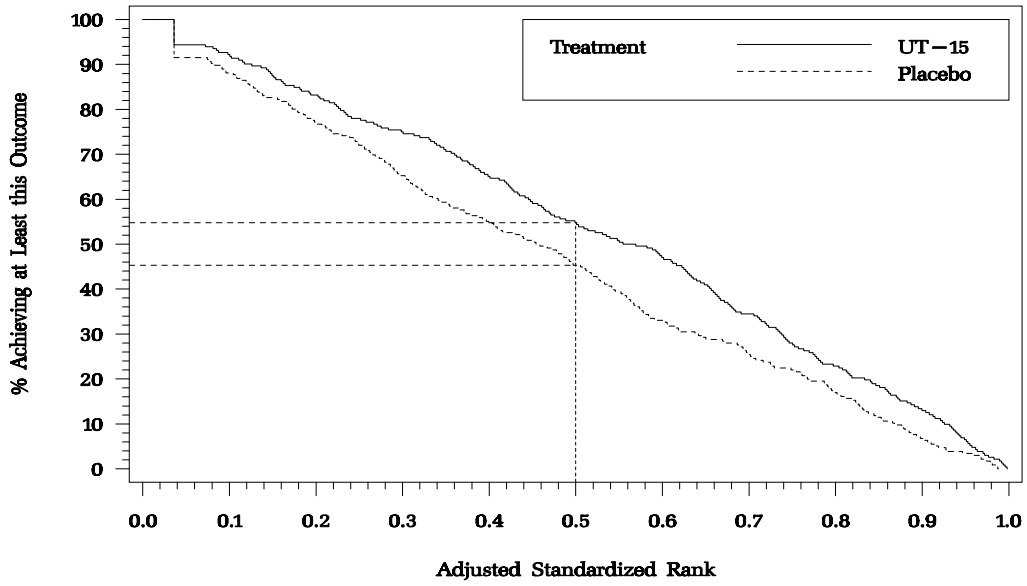
There was a relationship between the dose achieved after 12 weeks of double-blind treatment and the change in 6-minute walk distance, Table 3.6.1B. The higher the dose achieved, the better the increase in six-minute walk distance. A similar correlation was observed between plasma levels of treprostinil and the change in 6-minute walk distance at week 12.

Table 3.6.1B Relation of Effect on 6-Minute Walk Distance to Dose of Treprostinil at Week 12 (Pooled P01:04/05)

Treprostinil Dose		Mean Change in Walk Distance (m)
Quartiles	**Dose Range (ng/kg/min)**	
Below 25th Percentile	<5.0	-3.6
25th Percentile to < Median	5.0 to <8.2	6.6
Median to < 75th Percentile	8.2 to <13.8	14.6
75th Percentile and above	≥13.8	35.5

Although a single estimate is often used to describe the magnitude of a treatment effect, a more complete picture is provided by examining differences in the distribution of patient responses in the treatment groups. Figure 3.6.1A shows a plot of the adjusted standardized rank of change from baseline for the 6-minute walk distance. The P-value of 0.0064 for the pooled analysis (which is based on a nonparametric analysis adjusted for baseline walk, etiology and vasodilator use) is in fact based on this between-treatment comparison of adjusted standardized ranks. An adjusted standardized rank of 0.5 defines the 50% of patients who achieved that rank or better and an adjusted standardized rank of 0.75 defines the 25% of patients who achieved that rank or better. As shown across the range of ranks (particularly from 0.2 to 0.8), approximately 10% more treprostinil patients than placebo patients achieved any given rank or better.

Figure 3.6.1A Adjusted Standardized Rank of Change From Baseline for Exercise Capacity at Week 12.



Although these results did not quite meet the criteria specified in the statistical plan (pooled $P < 0.01$ with one of the two trials with a $P < 0.05$), the Division and the sponsor are in agreement with the conclusion that these results are indicative of a treatment effect of treprostinil in the management of patients with pulmonary arterial hypertension. However, the Division has characterized this treatment effect as small, reflecting approximately a 5% improvement from baseline. The sponsor does not disagree with this characterization, but notes that experience with the walk test across a variety of disorders has not yielded any consensus as to what increase in 6-minute walk distance constitutes a clinically meaningful change. In the absence of such information, the sponsor believes that alternative approaches should be used to gauge the clinical

meaningfulness of the observed treatment effect. Three approaches are possible: (1) quantifying the magnitude of the treatment effect in relevant subgroups; (2) evaluating both distance and symptoms in the assessment of exercise tolerance; and (3) observing the treatment effect on the principal reinforcing endpoints.

(1) - Treatment Effect in Subgroups

Before the blind of the trial was broken, a number of baseline covariates were selected with the intent of determining if these exerted a meaningful influence on the magnitude of the treatment effect (as assessed by the 6-minute walk test). The covariates selected included:

- Baseline exercise distance (continuous)
- NYHA classification (II vs. III vs. IV)
- Disease etiology (PPH vs. connective tissue disease vs. congenital shunts)
- Gender (male vs. female)
- Race (Caucasian vs. African origin vs. Hispanic vs. Other)
- Age (continuous and grouped [<16, 16-64, >64])
- Center
- Geographic regions (North America vs. rest of world)
- Baseline hemodynamics (CO, PAPm, PVRI, SVO_2)
- Concomitant medications (vasodilators, anticoagulants, diuretics and digoxin)

A summary of the covariate interactions are shown in Table 3.6.1C. The large majority of covariates tested were not significant ($p>0.1$), but those that reflected the clinical severity of pulmonary arterial hypertension (baseline walk distance, NYHA Class and SvO_2) appeared to have an important influence on the magnitude of the improvement produced by treprostinil.

Table 3.6.1C Summary of Covariate Interactions with Treatment in Analyses of 6-Minute Walk Test at Week 12 (Pooled 04/05 Data)

Covariate Analysis	**P-value**[a] *Pooled 04/05*
Baseline walk distance	**0.0338**
NYHA classification	**0.1051**
Disease etiology	0.5985
Gender	0.4278
Race	0.8302
Age Continuous variable Grouped (<16, 16-64, >64 yrs)	 0.3843 0.9488
Center	0.5709
Vasodilator use at baseline	0.3427
Geographic region	0.8196

Hemodynamics at baseline	
PAPm	0.3855
PVRI	0.5333
CI	0.2677
SVO_2	**0.0728**
Chronic concomitant medications	
Chronic vasodilator use	0.2880
Chronic anticoagulant use	**0.0416**
Chronic diuretic use	0.8637
Chronic digoxin use	0.9699

[a] P-values from the test of treatment by covariate interaction term in a parametric linear model using an alternative imputation method to correct violation of regression assumptions

In general, the more advanced the underlying disease, the more marked the response to treatment with treprostinil. This pattern is noteworthy because trials of new treatments for pulmonary arterial hypertension have restricted enrollment to patients with class III or IV symptoms. As shown in Table 3.6.1D, if such an approach had been followed in the major trials with treprostinil, the data support that the magnitude of the treatment effect would have been nearly two-three times greater than that actually observed (when class II patients were included in the analysis).

Table 3.6.1D Influence of Baseline Walk Distance, NYHA Class and SVO2 on the Response to Treprostinil (as Assessed by 6-Minute Walk Distance at 12 Weeks)

	Treatment Effect[a] (treprostinil – Placebo) mean ± SE	**p-value**
Baseline Walk at		
150m	51.15 ±16.33	0.0019
250m	33.42 ± 9.51	0.0005
350m	15.69 ± 7.27	0.0314
450m	-2.04 ± 12.40	0.8697
NYHA Classification		
II	-12.52 ± 20.68	0.5455
III	21.63 ± 7.69	0.0051
IV	56.41 ± 25.55	0.0278
Baseline SVO_2		
40%	43.58 ± 16.14	0.0072
50%	31.29 ± 10.54	0.0032
60%	19.01 ± 7.40	0.0106
70%	6.73 ± 9.58	0.4830
80%	-5.56 ± 14.90	0.7093

[a]As predicted from a linear regression model using an alternative imputation method to correct for violation of regression assumptions

(2) - Combined Assessment of Distance and Symptoms

The intent of the 6-minute walk test is to determine how much patients can do during the course of carrying out activities of daily living. However, the capacity of patients to function is determined not only by what they can do when they exert themselves to the fullest, but also by how they feel when they are carrying out their usual activities of daily living. Two patients may show an equal ability to walk down the street, but their clinical status is not equal if one walks with ease and the other walks while huffing and puffing.

It is therefore important not only to look at the distance traversed during the 6-minute walk but also the symptoms experienced at the end of the effort. Indeed, the investigator who played the key role in the development of the 6-minute walk test (Dr. Gordon Guyatt) has strongly recommended that symptoms and distance always be assessed together during the test.[9] In designing the pivotal trials with treprostinil, United Therapeutics prospectively followed Dr. Guyatt's guidance to assess performance and symptoms at the same time. In both study P01:04 and in study P01:05, patients were asked to report the magnitude of dyspnea using the Borg Dyspnea score at the completion of the 6-minute walk test. In fact, this score was specified as a secondary endpoint because we intended that it be used to interpret the results of the primary endpoint. At the completion of the 6-minute walk test, patients were asked to report the magnitude of dyspnea. The results (Table 3.6.1E) demonstrate that treprostinil ameliorates the magnitude of dyspnea experienced during the 6-minute walk test. Therefore, treatment with treprostinil enhances exercise tolerance by lessening symptoms despite an increase in work performed.

Table 3.6.1E Summary of Borg Dyspnea Scores: Change from Baseline at Week 12

Analysis Population Treatment Group	Borg Dyspnea Scores - Change from Baseline at Week 12 Mean ± SE (N)
Pooled 04/05	
Treprostinil	-0.88 ± 0.14 (201)
Placebo	+0.11 ± 0.17 (212)
p-value [a]	<0.0001
Study P01:04	
Treprostinil	-0.89 ± 0.18 (97)
Placebo	+0.10 ± 0.22 (100)
p-value	0.0006
Study P01:05	
Treprostinil	-0.88 ± 0.22 (104)
Placebo	+0.13 ± 0.27(112)
p-value	0.0010

[a] p-value from a Wilcoxon Rank Sum test.

To achieve the most comprehensive assessment possible of the effect of treprostinil on exercise capacity, we combined both assessments carried out during the 6-minute walk test (the primary endpoint) into a single analysis. This analysis accounts for the

interdependence of the change in walk distance and the change in effort (as measured by the Borg score) in evaluating the effect of treprostinil on the ability of patients to exercise. To do so, changes in both the 6-minute walk distances and Borg scores at the end of double-blind treatment (at 1, 6 and 12 weeks) were simultaneously compared between treatment groups using nonparametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test (analogous to the primary analysis methodology). The details of this methodology are presented in Appendix C.

The rationale behind this analysis is straight-forward, i.e., to rank a patient's overall exercise outcome, both the rank of the distance outcome and symptom outcome should be taken into account by calculating their average. For example, if a patient had a rank of 0.5 for walk distance (indicating that their adjusted change from baseline was at the median of the distribution of all walk changes), but a rank of 0.9 for Borg score (indicating that they had a highly favorable change in their Borg score), their combined rank would be 0.7, which corresponds to an overall outcome at the 70th percentile across all patients. Conversely, a highly favorable walk change would be mitigated (or even nullified) by an unfavorable change in Borg score.

The results for Weeks 1, 6 and 12 are presented in Figures 3.6.1B, 3.6.1C and 3.6.1D, respectively. The vertical axis on each plot represents the proportion of patients within each treatment group who received a combined rank of at least the corresponding value on the horizontal axis. The vertical separation between these curves represents the proportion of patients in each treatment group who achieved any given level of response. As can be seen by comparing the effect at Weeks 1, 6 and 12, the magnitude of separation between the two treatment groups increased as a function of the duration of treatment with treprostinil. At the end of double-blind therapy (Figure 3.6.1D), about 60% of patients in the treprostinil group but only about 40% of patients in the placebo group had a combined rank of at least 0.5 (the median combined response). This vertical separation of 20% is approximately twice the separation between treatment groups that was seen when the 6-minute walk was used as the sole measure of clinical effect.

This analysis reveals that a much larger proportion of patients benefited from treatment with treprostinil than can be envisioned based on an assessment of walk distance alone. It is also noteworthy that the P values for this analysis of the treatment effect were P=0.0011 for study P01:04 and P= 0.0024 for study P01:05, and the P value for the two trials combined was P=0.0000084. Hence, when both components of the exercise capacity are considered together, the treatment effect associated with the use of treprostinil is larger, more consistent and more meaningful than an analysis of walk distance alone. If one focused only on 6-minute walk distance (without considering the Borg scores), one would observe the treatment effect but would fail to appreciate the true impact of treatment on the ability of patients to tolerate exercise or on their overall sense of well-being.

Figure 3.6.1B Combined Rank Analysis of Changes in 6-Minute Walk Distance and Borg Dyspnea Score at Week 1

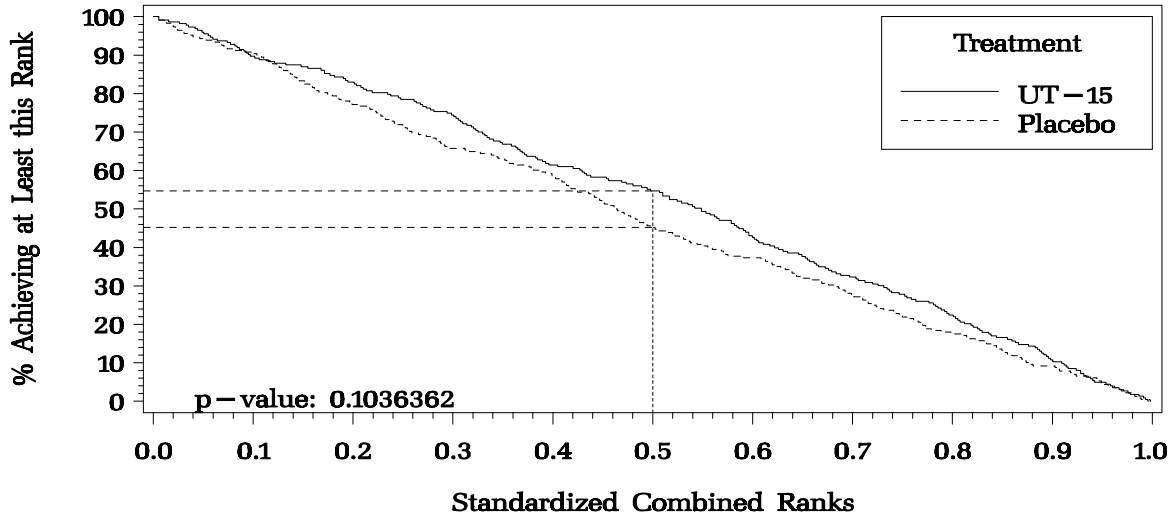


Figure 3.6.1C Combined Rank Analysis of Changes in 6-Minute Walk Distance and Borg Dyspnea Score at Week 6

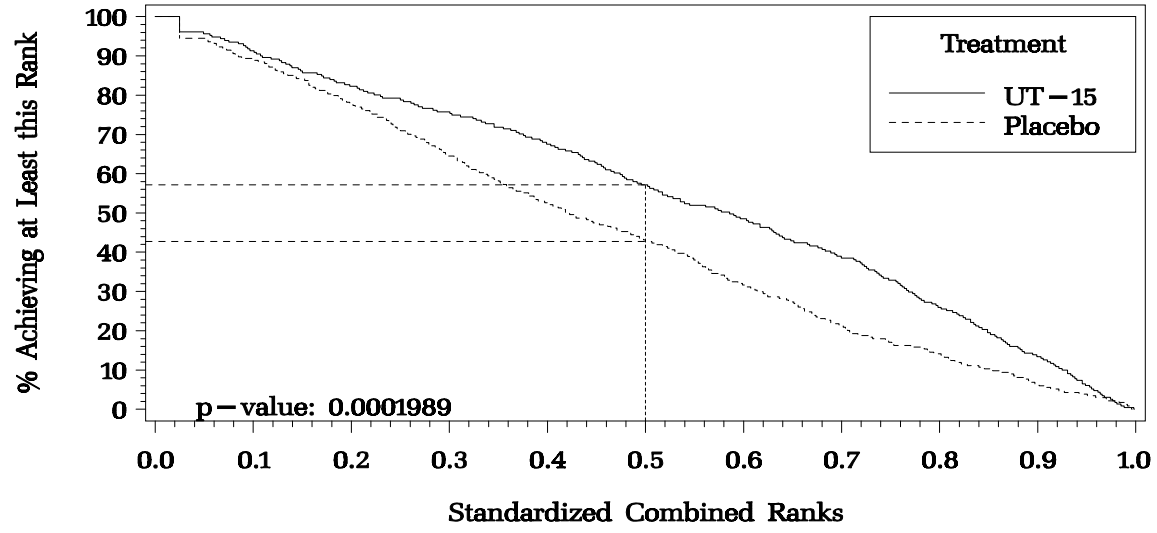
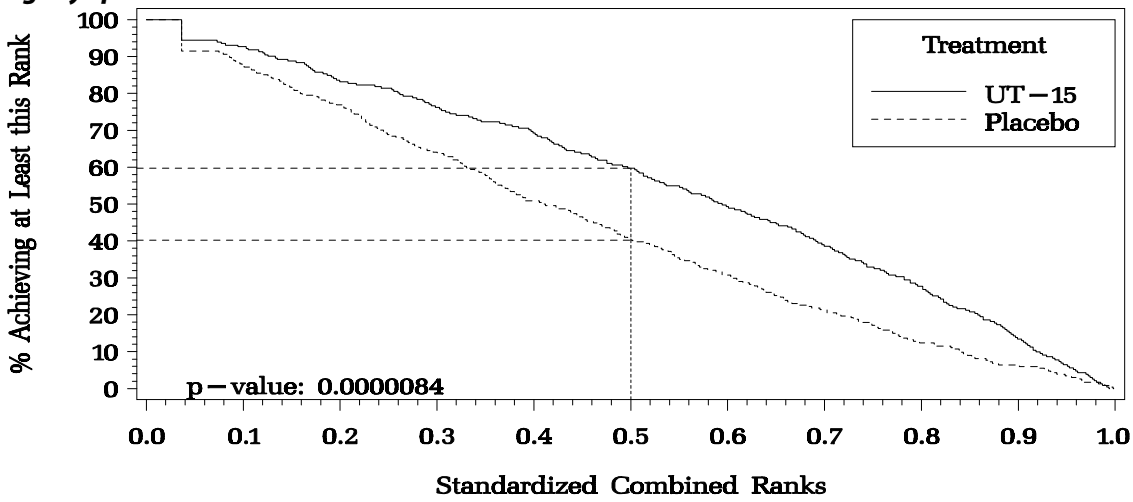


Figure 3.6.1D Combined Rank Analysis of Changes in 6-Minute Walk Distance and Borg Dyspnea Score at Week 12



(3) - Contribution of Principal Reinforcing Endpoints

The first two approaches to assessing the clinical meaningfulness of the treatment effect of treprostinil focused on measurements carried out during the 6-minute walk test. However, it was the sponsor's intent to utilize additional measures of efficacy (in addition to the effects on the primary endpoint) in judging the efficacy of treatment. As a result, the sponsor took the unusual step of prespecifying three principal reinforcing endpoints, which were intended to have priority over other secondary measures of the treatment effect. As shown below, treprostinil produced consistent and important improvements in the principal reinforcing endpoints related to symptoms and signs of heart failure and the dyspnea-fatigue rating. These additional data — when taken together with the information on exercise tolerance (as assessed by both distance and symptoms) — provide strong evidence that the effect of treprostinil in patients with pulmonary arterial hypertension is clinically meaningful.

3.6.2 Principal Reinforcing Endpoints

3.6.2.1 Symptoms and Signs of Pulmonary Hypertension

The first of the principal reinforcing endpoints was the assessment of symptoms and signs of pulmonary hypertension. The assessment of symptoms is the most direct and clinically meaningful way of evaluating clinical status, since the assessment of symptoms and signs mimics precisely the usual interaction that occurs between patients and physicians during a routine office visit. In addition, this approach allows for the evaluation of symptoms that occur spontaneously or at rest, including those that are not related to or evoked by exercise (and thus do not limit exercise tolerance).

A total of 8 symptoms and 8 physical signs were evaluated in each of the two major trials. Patients were asked about the presence or absence of each symptom and sign at the start of the study (before randomization) and again at the end of double-blind treatment. In completing this part of the case report form, investigators were not able to report symptoms that had improved but had not resolved. Similarly, this part of the case report form was designed to only detect symptoms that developed for the first time during the study but not symptoms that were originally present but had deteriorated.

To facilitate analysis of these data, the sponsor prespecified that information regarding the emergence or resolution of symptoms and signs were to be combined into a single score. Each symptom or sign was assigned a value of –1, 0 or +1, depending on whether the symptom or sign had emerged (-1) or resolved (+1). If the symptom or sign was present at both the start and end of the study (or was absent at both the start and end of the study), a value of 0 was assigned (even if the symptom or sign had improved or deteriorated). The values of the 16 symptoms and signs were summed to yield a composite score.

As shown in Table 3.6.2.1A., treprostinil therapy was associated with a significant improvement in the composite score of symptoms and signs of pulmonary hypertension after 12 weeks. This effect was apparent when studies P01:04 and P01:05 were considered individually or combined.

Table 3.6.2.1A Change in Composite Score Reflecting Signs and Symptoms of Pulmonary Hypertension After 1, 6 and 12 Weeks of Treatment

Analysis Population Treatment Group	Improvement from Baseline Mean ± SE (N)		
	Week 1	**Week 6**	**Week 12**
Pooled 04/05			
Treprostinil	0.8± 0.12 (230)	1.0 ± 0.15 (216)	0.9 ± 0.16 (201)
Placebo	0.6 ± 0.11 (233)	0.3 ± 0.13 (227)	-0.1 ± 0.15 (217)
p-value[a]	0.2460	0.0048	<0.0001
Study P01:04			
Treprostinil	0.9 ± 0.19 (111)	1.2 ± 0.23 (107)	0.9 ± 0.26 (97)
Placebo	0.7 ± 0.19 (110)	0.4 ± 0.19 (107)	-0.1 ± 0.22 (103)
p-value	0.7197	0.0178	0.0107
Study P01:05			
Treprostinil	0.8 ± 0.16 (119)	0.8 ± 0.19 (109)	1.0 ± 0.20 (104)
Placebo	0.5 ± 0.13 (123)	0.3 ± 0.16 (120)	-0.0 ± 0.20 (114)
p-value	0.1880	0.1152	0.0004

[a]P-value from a Wilcoxon rank sum test.

The sponsor recognizes that the composite score (although prespecified before the blind was broken) represents an arbitrary approach to the analysis of these data — an approach that assumes that all symptoms and signs have the same clinical weight. From both a clinical and regulatory perspective, such an assumption is not likely to be valid, since changes in symptoms (which are experienced by the patient) are more

clinically relevant than changes in signs (which are primarily apparent to the physician). Indeed, from a regulatory perspective, changes in physical signs might be viewed as surrogate markers and not as direct measures of patient benefit. It is therefore important not only to evaluate the effect of treprostinil on a composite score but also on the individual symptoms that characterize patients with pulmonary hypertension. The effect of treatment on individual symptoms at Week 12 is summarized in Table 3.6.2.1B. The data are displayed as the number resolved or developed in the numerator over the number of patients in whom the symptom could resolve (i.e., present at baseline) or develop (i.e. absent at baseline).

Table 3.6.2.1B. Changes in Individual Symptoms at Week 12 (Pooled P01:04/05)

	Placebo		Treprostinil		
	Resolved	Developed	Resolved	Developed	P Value
Dyspnea	4/219	1/2	8/201	0/0	0.122
Fatigue	12/189	12/32	17/182	5/19	0.063
Chest pain	37/82	30/139	48/82	8/119	0.002
Dizziness	35/98	33/123	55/100	27/101	0.021
Syncope	11/17	7/204	15/16	1/185	0.062
Orthopnea	14/65	30/155	29/60	17/141	0.003
Edema	25/101	29/120	36/81	18/120	0.028
Palpitations	25/92	22/129	46/102	27/99	0.100

The symptom data reveal an interesting pattern. In patients assigned to placebo, for most symptoms, the number of patients who developed the symptom was generally about the same as the number of patients in whom the symptom resolved — a pattern consistent with no overall net benefit. In contrast, in patients assigned to treprostinil, for each symptom, the number of patients in whom the symptom resolved greatly exceeded the number in whom it appeared during the course of double-blind treatment. Differences in the distribution of responses always favored treprostinil with nominal P values for the pooled data generally ≤ 0.10 (despite the low power of these individual symptom analyses). The consistency of the response in favor of treprostinil across all symptoms of pulmonary hypertension is noteworthy, particularly since the responses in this table reflect the complete resolution of old symptoms or emergence of new symptoms rather than reports of partial improvement or deterioration.

In its review of these data, the FDA has raised the possibility that the data shown in Table 3.6.2.1B may have been influenced by partial degrees of unblinding as a result of a predilection of treprostinil to cause infusion site reactions or pain. The sponsor understands that presumptions about the identity of the study medication (based on recognition of a characteristic adverse effect) could lead both patients and physicians to report some improvement in symptoms based on expectations that the study medication must be exerting some benefit. However, this type of unblinding is unlikely to account

for the results shown in Table 3.6.2.1B. To obtain the data in Table 3.6.2.1B, patients were not asked if symptoms had improved or worsened but were asked if symptoms were present or absent. Thus, patients could only identify and report symptoms that had appeared for the first time or resolved completely since the previous visit.

Could unblinding have influenced the results under these conditions? The sponsor believes that this is unlikely for three reasons:

1. Although it is possible to imagine that unblinding could lead patients to report varying degrees of improvement, unblinding is unlikely to lead to reports of complete resolution. Reports of complete resolution were consistently more common in the treprostinil group.

2. Even if one could envision scenario #1, it is even more unlikely that unblinding would lead a patient to fail to report a new symptom that had not been previously experienced. Reports of the new development of symptoms were consistently less common in the treprostinil group.

3. Even if one could envision scenario #2, it is important to recognize that symptoms vary in their ability to be influenced by the occurrence of unblinding. Many of the symptoms listed in Table 3.6.2.1B are subjective, but some (e.g., syncope) represent objective events and not simply reports of patient impressions. It is therefore noteworthy that syncope developed for the first time in 7 patients in the placebo group but only one patient in the treprostinil group.

3.6.2.2 Dyspnea-Fatigue Rating

Patients treated with treprostinil experienced a progressive improvement in the dyspnea-fatigue rating during the 12-week treatment period that was not seen in the placebo group. The difference between placebo and treprostinil was significant at the end of double-blind treatment, and at Week 6, whether the studies were considered together or individually, Table 3.6.2.2.

Table 3.6.2.2 Change in Dyspnea-Fatigue Rating

	Change from Baseline Mean ± SE (N)		
	Week 1	**Week 6**	**Week 12**
Pooled 04/05			
Treprostinil	0.21 ± 0.08 (229)	0.79 ± 0.12 (218)	1.23 ± 0.13 (201)
Placebo	0.02 ± 0.08 (233)	0.19 ± 0.11 (227)	- 0.14 ± 0.13 (216)
p-value[a]	0.0170	0.0001	<0.0001
Study P01:04			
Treprostinil	0.23 ± 0.14 (111)	0.85 ± 0.18 (108)	1.15 ± 0.18 (97)
Placebo	0.14 ± 0.13 (110)	0.11 ± 0.17 (107)	- 0.24 ± 0.21 (102)
p-value	0.3637	0.0023	<0.0001
Study P01:05			
Treprostinil	0.19 ± 0.09 (118)	0.74 ± 0.16 (110)	1.30 ± 0.19 (104)
Placebo	- 0.08 ± 0.08 (123)	0.27 ± 0.14 (120)	- 0.06 ± 0.15 (114)
p-value	0.0106	0.0184	<0.0001

[a]P-value from a Wilcoxon Rank Sum test.

Although the New York Heart Association (NYHA) functional class was not specifically assessed in study P01:04 or P01:05, one component of the dyspnea-fatigue rating (Magnitude of Task) closely resembles the NYHA classification. This component asks physicians to rank the patients' functional capacity according to a 5-point scale:

- Becomes symptomatic only with extraordinary activity
- Becomes symptomatic only with major activities
- Becomes symptomatic only with moderate or average tasks
- Becomes symptomatic only with light activities
- Symptomatic at rest

Of note, an improvement in at least one activity level was observed at Week 12 in 40% of the patients in the treprostinil group as compared with only 15% of the patients in the placebo group.

3.6.2.3 Deaths, Transplantation or Discontinuation Due to Clinical Deterioration

The frequency of death, transplantation, or discontinuation from study drug due to clinical deterioration was similar between the two treatment groups, Table 3.6.2.3. Although studies P01:04 and P01:05 were too small and brief to provide definitive data on morbidity and mortality, these data do not suggest an adverse effect of treprostinil on the natural history of pulmonary arterial hypertension.

Table 3.6.2.3 Mortality, Transplantation and Discontinuation of Study Drug Due to Clinical Deterioration

Events	Number of Patients (%)			
	Treprostinil **Pooled – 233** 01:04 – 113 01:05 – 120	**Placebo** **Pooled – 236** 01:04 – 111 01:05 - 125	**Odds Ratio**	**95% CI**
Deaths Within 12 Weeks Regardless of Transplant, Deterioration or AE.	**9 (3.9)** 4 (3.5) 5 (4.2)	**10 (4.2)** 5 (4.5) 5 (4.0)	**0.91** 0.78 1.04	**0.3621, 2.2769** 0.2034, 2.9762 0.2943, 3.6997
Deaths While in Study	**7 (3.0)** 4 (3.5) 3 (2.5)	**7 (3.0)** 4 (3.6) 3 (2.4)	**1.01** 0.98 1.04	**0.3498, 2.9354** 0.2393, 4.0262 0.2063, 5.2705
Deaths or Transplantation	**9 (3.9)** 4(3.5) 5(4.2)	**11 (4.7)** 6 (5.4) 5 (4.0)	**0.82** 0.64 1.04	**0.3341, 2.0217** 0.1762, 2.3405 0.2943, 3.6997
Deaths or Transplantation or Discontinuation of Study Drug Due to Clinical Deterioration	**13 (5.6)** 5 (4.4) 8 (6.7)	**16 (6.8)** 8 (7.2) 8 (6.4)	**0.81** 0.60 1.05	**0.3818, 1.7292** 0.1888, 1.8815 0.3791, 2.8787

3.6.3 Other Efficacy Measures

3.6.3.1 Hemodynamic Effects

After 12 weeks of treatment, treprostinil produced significant increases in cardiac output and decreases in pulmonary and systemic vascular resistances, mean pulmonary artery and mean right atrial pressures with little change in systemic blood pressure or heart rate (Table 3.6.3.1). Hence, treprostinil therapy was associated with the hemodynamic profile that would be expected for an effective drug for the treatment of pulmonary arterial hypertension.

Table 3.6.3.1 Change in Hemodynamic Variables After 12 Weeks

	Change from Baseline After 12 Weeks (Mean ± SE)		
Parameter	**Treprostinil** Pooled: N = 163-199 04: N = 77-95 05: N = 87-104	**Placebo** Pooled: N = 182-215 04: N = 86-103 05: N = 96-112	**P-value[a]**
HR (bpm)	-0.5 ± 0.80 -1.1 ± 1.08 +0.1 ± 1.17	-0.8 ± 0.74 -1.8 ± 1.02 -0.2 ± 1.07	0.5133 0.6789 0.5677
RAPm (mmHg)	-0.5 ± 0.36 -0.2 ± 0.52 -0.7 ± 0.49	+1.4 ± 0.33 +1.3 ± 0.52 +1.3 ± 0.42	0.0002 0.0649 0.0005
CI (L/min/m^2)	+0.12 ± 0.04 +0.12 ± 0.06 +0.12 ± 0.06	-0.06 ± 0.04 -0.07 ± 0.06 -0.05 ± 0.05	<0.0001 0.0049 0.0082

PAPm (mmHg)	-2.3 ± 0.51 -1.7 ± 0.74 -2.9 ± 0.71	+0.7 ± 0.58 +0.1 ± 0.86 +1.0 ± 0.75	0.0003 0.1166 0.0006
PVRI[b] (mmHg/L/min/m^2)	-3.54 ± 0.64 -3.64 ± 0.97 -3.43 ± 0.84	+1.20 ± 0.57 +0.96 ± 0.99 +1.45 ± 0.65	<0.0001 0.0004 <0.0001
SAPm (mmHg)	-1.7 ± 0.86 -0.7 ± 1.25 -2.6 ± 1.18	-1.0 ± 0.91 -1.0 ± 1.40 -1.0 ± 1.18	0.2739 0.4172 0.4500
SVRI[c] (mmHg/L/min/m^2)	-3.54 ± 0.96 -4.78 ± 1.47 -2.29 ± 1.20	-0.80 ± 0.85 -0.87 ± 1.43 -0.71 ± 1.00	0.0012 0.0058 0.1037
SvO_2 (%)	+2.0 ± 0.76 +2.3 ± 1.08 +1.8 ± 1.08	-1.4 ± 0.65 -1.9 ± 1.06 -1.0 ± 0.79	0.0001 0.0126 0.0035

[a]P-value from ANCOVA (mITT group) adjusting for Baseline value.
[b]PVRI (mmHg/L/min/m2) = [PAPm-PCWP] / CI for patients without intracardiac shunts; for patients with unrepaired intracardiac shunts, pulmonary blood flow was used as the flow parameter.
[c]SVRI (mmHg/L/min/m^2) = [SAPm-RAPm] / CI for patients without intracardiac shunts; for patients with unrepaired intracardiac shunts, pulmonary blood flow was used as the flow parameter

3.6.3.2 Quality of Life Assessment

The effects of treprostinil on the Minnesota Living with Heart Failure Questionnaire are shown in Table 3.6.3.2. It should be noted that a number of patients did not have this evaluation because this measure was added at the Agency's request as a protocol amendment after enrollment had been initiated. [This is the reason why this instrument was not even designated as a secondary endpoint.] Thus, neither study P01:04 and study P01:05 was expected to have sufficient statistical power to detect a treatment effect when considered individually. Nevertheless, for the two trials combined, treprostinil produced significant improvements in the physical dimension (P = 0.0064) without adversely affecting the emotional dimension. The results of the individual studies were consistent with the pooled results. A similar pattern of physical but not emotional improvement has been seen in trials of effective drugs for the treatment of left heart failure.

Table 3.6.3.2 Change in Quality of Life Scores After 12 Weeks

	Quality of Life Scores Change from Baseline to Week 12 Mean ± SE		
	Global QOL	**Physical Dimension**	**Emotional Dimension**
Pooled 04/05			
Treprostinil (N=157)	-6.6 ± 1.61	-4.5 ± 0.73	-1.3 ± 0.47[b]
Placebo (N=173)	-1.9 ± 1.44	-1.8 ± 0.65	-0.3 ± 0.46
p-value [a]	0.1746	0.0064	0.3678
Study P01:04			
Treprostinil (N=65)	-5.0 ± 2.49	-4.3 ± 1.19	-1.1 ± 0.72
Placebo (N=69)	-1.2 ± 2.33	-1.4 ± 1.05	-0.8 ± 0.74
p-value	0.4345	0.0553	0.9840
Study P01:05			
Treprostinil (N=92)	-7.7 ± 2.12	-4.7 ± 0.93	-1.5 ± 0.62[c]
Placebo (N=104)	-2.9 ± 1.94	-2.2 ± 0.89	-0.2 ± 0.61
p-value	0.2869	0.0716	0.2480

[a] p-value from Wilcoxon Rank Sum test
[b] N=156
[c] N=91

3.7 Evidence for Long-Term Effectiveness

Long term efficacy (beyond 3 months) was not evaluated in prospectively designed, well controlled trials. Patients who completed any one of the three controlled trial were allowed to receive treprostinil in an uncontrolled long-term treatment study, P01:06; only adverse events, dosing and laboratory chemistry were formally evaluated. However, exercise testing was continued at periodic intervals at many of the centers and appeared to be maintained for the duration of follow-up (up to 21 months)[10], Table 3.7.

Table 3.7 Long-term Dosing and Exercise Data from Selected Centers in Study P01:06.

Month	**No. Patients (% of patients with specified duration of exposure)**	**Dose[a] (ng/kg/min)**	**Exercise: Change from Baseline (meters)**
Baseline	406 (64)	NA	334 ± 4.6
6	156 (38)	16 ± 0.7	+34 ± 6
9	112 (34)	19 ± 1.3	+34 ± 8
12	102 (37)	25 ± 1.7	+33 ± 7
15	63 (35)	24 ± 2.1	+37 ± 12
18	46 (43)	31 ± 3.1	+46 ± 13
21	15 (38)	38 ± 7.1	+55 ± 17

[a] Dose based only on patients with corresponding walk data

3.8 Conclusions Regarding Efficacy of Treprostinil

The results of two identical double-blind randomized controlled trials have shown that treprostinil produces favorable effects in patients with pulmonary arterial hypertension. These benefits are observed consistently across a wide variety of efficacy measures, are clinically meaningful and are apparent whether the trials are considered together or individually.

The evidence supporting the efficacy of subcutaneous treprostinil can be summarized as follows:

- Treprostinil produced an improvement in exercise capacity (primary endpoint) in patients with pulmonary arterial hypertension. Treatment led to an improvement in walk distance while reducing the severity of concomitant symptoms. These benefits were particularly striking in patients with the most severe symptoms at the start of treatment (class III and IV).

- Treatment with treprostinil alleviated many of the symptoms of pulmonary hypertension with little effect on the physical signs of the disease (a principal reinforcing endpoint). When compared with placebo, patients treated with treprostinil were more likely to have pre-existing symptoms resolve and were less likely to have symptoms develop for the first time. This was true across a broad range of symptoms, including those that constituted objective events (e.g., syncope) rather than subjective impressions (e.g., palpitations).

- Treprostinil produced an improvement in additional physician and patient assessments, including the physician-based dyspnea-fatigue rating (a principal reinforcing endpoint) and the physical domain of the Minnesota quality of life instrument (a patient-based evaluation). The pattern and magnitude of the response to treatment was similar to those seen with effective drugs for the management of left heart failure.

- Treprostinil was associated with sustained hemodynamic benefits that are characteristic of those believed to be required for successful treatment of pulmonary arterial hypertension.

These benefits were observed in an investigative environment that was specifically designed to minimize bias. Specifically, unlike earlier studies in pulmonary arterial hypertension, the studies were double-blind and utilized independent assessors of exercise performance (primary endpoint).

The totality and consistency of the findings indicate that the benefits of treprostinil are readily distinguishable from those of placebo and are clinically meaningful.

4 SAFETY OF TREPROSTINIL

4.1 Introduction

Treprostinil has been administered intravenously and subcutaneously to 843 patients or healthy volunteers in 15 clinical studies; of these, 743 patients with PAH were enrolled. This summary of the safety data with treprostinil will focus on studies related to the chronic subcutaneous administration of the drug in patients with pulmonary arterial hypertension; including placebo controlled studies P01:03, P01:04 and P01:05 and the open-label extension study, P01:06.

The primary measures of safety in these studies were reports of adverse events. Of important note, since there were no clinically meaningful changes in vital signs, in electrocardiographic intervals, in clinical chemistry or hematology indices, or in INR values seen in treprostinil-treated patients in placebo-controlled or open-label studies. Accordingly, these data are not reviewed in detail in this document.

4.2 Extent of Exposure

All patients completing the three controlled studies (P01:03, P01:04 and P01:05) had the option to receive treprostinil in the open-label extension study P01:06. The total chronic exposure to treprostinil is based on all patients who received treprostinil in studies P01:03, P01:04 and P01:05 (whether or not they entered P01:06) and P01:06; n=679 as of October 1, 2000 data cut-off. Of the 495 patients who received study medication in studies P01:03, P01:04 and P01:05, 445 patients were eligible to continue in the open-label study, of whom 423 (95%) elected to enter the open-label continuation protocol P01:06. In addition, 208 patients were enrolled directly into study P01:06 without having entered any earlier placebo-controlled trial. As a result, a total of 631 patients were enrolled into study P01:06.

Total chronic exposure to treprostinil for the 679 patients enrolled in chronic studies (P01:03, P01:04, P01:05, and P01:06) through October 1, 2000 was 483.5 patient-years (Table 4.2A). The mean number of patient-years of exposure is 0.7 years; the longest duration of exposure is more than 2 years.

Table 4.2A Duration of Exposure to Treprostinil in studies P01:03, P01:04 and P01:05, and P01:06 combined

DURATION OF EXPOSURE[a]	NUMBER OF PATIENTS (PERCENT EXPOSED)	
Total exposed to treprostinil	679	(100)
≥ 2 Weeks	652	(96)
≥ 4 Weeks	614	(90)
≥ 6 Weeks	586	(86)
≥ 8 Weeks	556	(82)
≥ 10 Weeks	531	(78)
≥ 12 Weeks	508	(75)
≥ 16 Weeks	455	(67)
≥ 20 Weeks	426	(63)
≥ 28 Weeks	374	(55)
≥ 36 Weeks	325	(48)
≥ 44 Weeks	279	(41)
≥ 52 Weeks	224	(33)
≥ 65 Weeks	128	(19)
≥ 78 Weeks	47	(7)
≥ 91 Weeks	18	(3)
≥ 104 Weeks	12	(2)
≥ 117 Weeks	1	(<1)
Total Patient-Days	**176,596**	
Total Patient-Weeks	**25,228**	
Total Patient-Years	**483.5**	

[a]Includes days on which treprostinil dosing was briefly interrupted.

The doses of treprostinil were adjusted over the duration of the study to reduce symptoms of pulmonary hypertension without producing intolerable adverse effects. The mean dose of treprostinil at initiation of treatment was 1.3 ng/kg/min. Doses of treprostinil were subsequently adjusted during the study. The doses used at each follow-up time are shown in Table 4.2B.

Table 4.2B Mean Dose of Treprostinil at the End of Specified Period (P01:06)

STUDY EVALUATION PERIOD[a]	MEAN DOSE ± SEM ng/kg/min (N)[b]	MAXIMUM DOSE ng/kg/min
Initiation	1.3 ± 0.0 (631)	12.5
Month 1	4.2 ± 0.1 (569)	35.0
Month 2	7.3 ± 0.2 (521)	55.0
Month 3	9.6 ± 0.3 (483)	65.0
Month 6	15.4 ± 0.5 (384)	55.0
Month 12	20.3 ± 0.7 (305)	65.0
Month 15	23.9 ± 1.0 (227)	70.0
Month 18	26.6 ± 1.5 (133)	85.0
Month 21	29.8 ± 2.5 (52)	87.0

[a] The term, study evaluation period, refers to time from treprostinil initiation in previous study if the patient was randomized to treprostinil; otherwise, this term refers to time from treprostinil initiation in open-label study.

[b] N = total number of patients receiving a dose > 0 ng/kg/min at the end of the month specified

Overall, the mean dose of treprostinil increased by approximately 3 ng/kg/min monthly for the first three months and then by approximately 1 ng/kg/min monthly during subsequent months. The mean dose of treprostinil after 21 months of therapy was approximately 30 ng/kg/min.

All patients had some modification to the dose of treprostinil during the study. As expected, there were more dose increases than dose decreases (Table 4.2C.). The number of dose increases were greatest during the first few months. Thereafter, the overall number of dose increases and dose decreases occurred much less frequently (≤ 1 per month) and remained generally stable over time.

Table 4.2.C Mean Number of Changes in the Dose of Treprostinil at Specified Times During Follow-Up in Study P01:06

STUDY EVALUATION PERIOD[a]	DOSE INCREASES	DOSE DECREASES
Month 1[b] – Overall: (N = 631)	4.6 ± 0.1	0.3 ± 0.0
Month 3[b] – Overall: (N = 522)	2.9 ± 0.1	0.4 ± 0.0
Month 6 – Overall: (N = 480)	5.8 ± 0.3	0.8 ± 0.1
Month 12 – Overall: (N = 383)	3.8 ± 0.2	0.6 ± 0.1
Month 15 – Overall: (N = 305)	2.7 ± 0.2	0.6 ± 0.1
Month 18 – Overall: (N = 228)	1.8 ± 0.2	0.8 ± 0.1
Month 21 – Overall: (N = 133)	1.5 ± 0.2	1.3 ± 0.2
Month 24 – Overall: (N = 51)	1.7 ± 0.3	1.3 ± 0.1

Shown are means ± SE.

[a] The term, study evaluation period, refers to time from treprostinil initiation in previous study if the patient was randomized to treprostinil; otherwise, this term refers to time from treprostinil initiation in open-label.

[b] This time point included a duration one month (Days 1-30 or 61-90) whereas each evaluation period for Months 6-24 included a duration of three months.

4.3 Adverse Events

Nearly all patients enrolled in studies P01:03, P01:04, P01:05 and P01:06 experienced an adverse event; adverse events that were regarded as drug-related or severe were more frequent in the treprostinil group than in the placebo group, Table 4.3. Hence, more patients in the treprostinil group required early discontinuation of treatment due to an adverse event (10% vs 3%). However, the frequency of serious adverse events (and deaths) was similar in the two treatment groups. During the open-label extension study, the frequency and severity of adverse events was similar to that seen in patients receiving active therapy in the placebo controlled trials, even though the duration of exposure in the open-label studies far exceeded that in the controlled trials.

Table 4.3 Frequency and Characteristics of Adverse Events Reported in Long-term Studies (Placebo-Controlled and Open-Label Studies)

	Number (%) of Patients		
	03/04/05 Treprostinil (N=253)	**03/04/05 Placebo (N=242)**	**P01:06 Treprostinil (N=631)**
Treatment-emergent AEs			
All AEs	248 (98)	226 (94)	599 (95)
Drug-related[a] AEs	245 (97)	161 (67)	581 (92)
Severe AEs			
All	159 (63)	50 (21)	324 (51)
Drug-related[a]	147 (58)	15 (6)	240 (38)
Serious AEs			
All SAEs	44 (17)	38 (16)	170 (27)
Drug-related SAEs	11 (4)	2 (1)	25 (4)
Patients who required early discontinuation due to AEs or SAEs	26 (10)	7(3)	96 (15)
Deaths[b]	9 (4)	10 (4)	36 (6)

[a] 'Drug-related' is possibly or reasonably attributable to study drug as judged by the investigator.
[b] Includes death during the 12-Week Study period, whether or not the patient was receiving treprostinil (intention-to-treat for planned duration of treatment).

4.3.1 Frequency and Relation to Treatment

The most common adverse events regardless of cause (Table 4.3.1A) and adverse events judged possibly or reasonably attributable to treprostinil (Table 4.3.1B) are shown in the tables below. Adverse events that were nominally more common in patients receiving treprostinil included infusion site pain or reaction, diarrhea, headache, nausea, jaw pain, vasodilatation, edema and anorexia. All of these have been identified as characteristic adverse effects of prostaglandin therapy in earlier studies. During the open-label extension study, the pattern and frequency of adverse events was similar to that seen in patients receiving active therapy in the placebo controlled trials, even though the duration of exposure in the open-label studies far exceeded that in the controlled trials.

Table 4.3.1A. Treatment-Emergent Adverse Events (Regardless of Attributed Cause) Reported by > 10% of Patients in Placebo-Controlled and Open-Label Studies

	Number (%) of Patients		
	03/04/05 Treprostinil (N=253)	**03/04/05 Placebo (N=242)**	**P01:06 (N=631)**
Infusion site pain	215 (85)	64 (26)	526 (83)
Infusion site reaction	212 (84)	64 (26)	482 (76)
Infusion site bleed/bruise	84 (33)	104 (43)	163 (26)
Diarrhea	68 (27)	37 (15)	184 (29)
Headache	78 (31)	58 (24)	132 (21)
Nausea	62 (25)	42 (17)	145 (23)
Jaw pain	38 (15)	12 (5)	98 (16)
Pain[a]	35 (14)	25 (10)	92 (15)
Dizziness	23 (9)	20 (8)	71 (11)
Rash	33 (13)	26 (11)	70 (11)
Pharyngitis	14 (6)	22 (9)	74 (12)
Vasodilatation	33 (13)	12 (5)	59 (9)

[a] This term captures all reports of aches, cramps, or pains which were not reported as pain at the defined sites of abdomen, back, breast, chest, flank, injection site, neck, or pelvis.

Table 4.3.1.B Treatment-Emergent Adverse Events (Reasonably or Possibly Attributable to the Study Drug) Reported by > 5% of Patients in Placebo-Controlled and Open-Label Studies

	Number (%) of Patients		
	03/04/05 Treprostinil (N=253)	**03/04/05 Placebo (N=242)**	**P01:06 (N=631)**
Infusion site pain	215 (85)	60 (25)	526 (83)
Infusion site reaction	212 (84)	53 (22)	479 (76)
Diarrhea	60 (24)	24 (10)	170 (27)
Headache	69 (27)	29 (12)	115 (18)
Nausea	54 (21)	26 (11)	124 (20)
Infusion site bleed/bruise	54 (21)	52 (22)	95 (15)
Jaw pain	36 (14)	10 (4)	96 (15)
Pain[a]	30 (12)	14 (6)	77 (12)
Vasodilatation	31 (12)	10 (4)	51 (8)
Rash	27 (11)	16 (7)	54 (9)
Dizziness	12 (5)	10 (4)	47 (7)
Pruritus	16 (6)	6 (3)	31 (5)
Edema	18 (7)	2 (1)	20 (3)
Vomiting	14 (6)	7 (3)	24 (4)
Anorexia	10 (4)	2 (1)	35 (6)

[a] This term captures all reports of aches, cramps, or pains which were not reported as pain at the defined sites of abdomen, back, breast, chest, flank, injection site, neck, or pelvis.

4.3.2 Relation of Adverse Events to Dose and Duration of Exposure

In all of the long-term studies with treprostinil, initial exposure to study drug was always at a dose of approximately 1.25 ng/kg/min and higher doses were subsequently achieved only during prolonged exposure to study drug. As a result, it is difficult to distinguish the influence of dose from that of duration on the frequency or severity of adverse events, particularly in studies where neither dose nor duration was randomly assigned. Despite these inherent limitations, analyses of the relation of adverse events to dose and duration of exposure are of interest.

Table 4.3.2A displays the dose of onset for all treatment-emergent adverse events that occurred in greater than 10% of the patients enrolled in Study P01:06. [Multiple occurrences of the same AE within a patient were counted only once by dose group according to the lowest dose at onset.] The onset of infusion site reactions and infusion site pain were reported most frequently at very low doses of treprostinil (e.g., ≤ 2.5 ng/kg/min). In contrast, other adverse events characteristic of therapy with treprostinil were generally seen with higher doses (e.g., > 10 ng/kg/min). These observations suggest that — among all of the adverse events related to treatment with treprostinil — the occurrence of infusion site pain/reaction is most likely related to the magnitude (and/or rapidity) of change in the infusion rate rather than the dose of the drug.

Table 4.3.2A Adverse Events Reported in >10% of Patients, Displayed by Dose at Onset, in Study P01:06

Adverse event	DOSES (ng/kg/min)							
	>0 to ≤2.5	**>2.5 to ≤5.0**	**>5.0 to ≤10.0**	**>10.0 to ≤20.0**	**>20.0 to ≤40.0**	**>40.0 to ≤60.0**	**>60**	**All**
# Patients Receiving Dose	624	543	486	385	208	60	14	631
Infusion Site Pain	296 (47)	84 (15)	98 (20)	77 (20)	13 (6)	2 (3)	0 (0)	520 (82)
Infusion Site Reaction	277 (44)	87 (16)	110 (23)	83 (22)	21 (10)	2 (3)	0 (0)	480 (76)
Diarrhea	38 (6)	21 (4)	41 (8)	57 (15)	29 (14)	5 (8)	1 (7)	183 (29)
Infusion Site Bleed/Bruise	84 (13)	34 (6)	26 (5)	30 (8)	9 (4)	0 (0)	0 (0)	162 (26)
Nausea	41 (7)	18 (3)	40 (8)	35 (9)	11 (5)	4 (7)	1 (7)	144 (23)
Headache	54 (9)	23 (4)	16 (3)	28 (7)	14 (7)	4 (7)	0 (0)	130 (21)
Jaw Pain	14 (2)	11 (2)	29 (6)	25 (6)	17 (8)	3 (5)	0 (0)	98 (16)
Pain	26 (4)	10 (2)	19 (4)	26 (7)	16 (8)	7 (12)	1 (7)	91 (14)
Pharyngitis	16 (3)	9 (2)	24 (5)	14 (4)	8 (4)	5 (8)	2 (14)	72 (11)
Dizziness	26 (4)	5 (1)	12 (2)	23 (6)	9 (4)	0 (0)	1 (7)	71 (11)
Rash	24 (4)	7 (1)	14 (3)	15 (4)	11 (5)	1 (2)	1 (7)	70 (11)

[a] This term captures all reports of aches, cramps, or pains which were not reported as pain at the defined sites of abdomen, back, breast, chest, flank, injection site, neck, or pelvis.

Multiple occurrences of the same AE within a patient were counted only once by dose group according to the lowest dose at onset.

A similar conclusion can be reached by analyzing the frequency of reports of adverse events as a function of the duration of treatment with treprostinil. All 254 patients who had complete safety data for at least 72 weeks were evaluated for the frequency of reports during specified time intervals, Table 4.3.2B. The analysis was confined to patients completing 72 weeks to minimize the possibility that the discontinuation of patients due to an adverse event may have created a bias that would have inaccurately decreased the frequency of reports of specific adverse events. For this analysis, if an adverse event occurred on Day 1 and continued through Week 48, it is recorded for each time interval except the final interval.

Table 4.3.2.B shows that the incidence of adverse events decreases with increasing duration of exposure. This was particularly true of localized events (infusion site pain and reaction), but it was also valid for systemic events (diarrhea, headache, nausea). These data are consistent with the hypothesis proposed based on the data presented in Table 4.3.2.A that the occurrence of infusion site pain/reaction is most likely related to

the magnitude (and/or rapidity) of change in the infusion rate rather than the absolute dose of the drug.

Table 4.3.2B. Frequency of Reports of Drug-Related Adverse Events Occurring in >10% of Patients Treated For At Least 72 Weeks During Specific Intervals of Follow-Up (P01:06); N=254.

Adverse Event	Day 1	Day 2 – Week 12	Weeks 13-24	Weeks 25-47	Weeks 48-72
Infusion site reaction	10%	83%	57%	47%	43%
Infusion site pain	12%	88%	54%	43%	39%
Diarrhea	2%	18%	15%	16%	12%
Headache	6%	21%	10%	12%	7%
Nausea	3%	15%	11%	11%	7%
Jaw Pain	1%	11%	9%	9%	6%
Pain[a]	1%	13%	7%	7%	6%
Infusion site bleed/bruise	6%	16%	7%	7%	5%
Vasodilatation	2%	11%	6%	4%	5%
Rash	2%	11%	4%	4%	3%

[a]This term captures all reports of aches, cramps, or pains which were not reported as pain at the defined sites of abdomen, back, breast, chest, flank, injection site, neck, or pelvis.

4.3.3 Adverse Events Leading to Reduction in Dose

The ability to increase dose was limited primarily due to the occurrence of an adverse event, primarily one related to the infusion site. Similarly, adverse experiences related to the infusion site were the most common reason for dose reduction (Table 4.3.3).

Table 4.3.3. Treatment-Emergent Adverse Events Requiring Dose Reduction (Occurring in ≥ 1% of Patients) in Study P01:06

COSTART Preferred Term	Number (%) of Patients Having Event
Infusion Site Pain	156 (25)
Infusion Site Reaction	56 (9)
Diarrhea	27 (4)
Nausea	25 (4)
Headache	23 (4)
Dizziness	12 (2)
Pain	11 (2)
Heart Failure	10 (2)
Vomiting	9 (1)
Hypotension	9 (1)
Jaw Pain	8 (1)
Vasodilation	8 (1)
Pulmonary Hypertension	7 (1)
Hypoxia	5 (1)
Asthenia	5 (1)
Edema	4 (1)
Abdominal Pain	4 (1)

4.3.4 Adverse Events Leading to Withdrawal of Treprostinil

About 15% of patients who were enrolled in placebo-controlled trials or in open-label studies discontinued treatment with treprostinil due to an adverse event. Infusion site pain was the most common reason for premature discontinuation (Table 4.3.4) leading to the withdrawal of treatment in about 7% of patients enrolled in studies P01:03, P01:04 and P01:05 (duration of treatment = 8-12 weeks) and in about 14% of patients enrolled in study P01:06 (mean duration of treatment = 9.6 months). Hence, with prolonged therapy, the rate of discontinuations due to infusion site pain diminishes considerably. Other reasons for premature discontinuation are very infrequent and were generally related to the underlying disease.

Table 4.3.4 Adverse Events Leading to Discontinuation of Study Drug in Two or More Patients in Long-Term Studies with Treprostinil (Placebo Controlled and Open Label Trials)

Adverse Experience	Number (%) of Patients		
	03/04/05 Treprostinil (N=253)	03/04/05 Placebo (N=242)	P01:06[b] (N=631)
Infusion site pain	17 (7)	0 (0)	88 (14)
Infusion site reaction	8 (3)	0 (0)	22 (3)
Heart failure	2 (1)	0 (0)	11(2)
Pulmonary hypertension	1 (<1)	4 (2)	6 (<1)
Infusion site bleed/bruise	2 (1)	0(0)	1 (<1)
Chest Pain	2 (1)	1 (<1)	1 (<1)
Pain[a]	0 (0)	0 (0)	2 (<1)
Shock	2 (1)	1 (<1))	0 (0)
Anxiety	2 (1)	0 (0)	0 (0)

[a] This term captures all reports of aches, cramps, or pains which were not reported as pain at the defined sites of abdomen, back, breast, chest, flank, injection site, neck, or pelvis.
[b] Includes patient data through October 1, 2000 cut-off date

4.4 Serious Adverse Events

4.4.1 General Considerations

In the long-term controlled studies P01:03, P01:04 and P01:05, serious adverse events were reported in 44 (17.4%) of the patients in the treprostinil group as compared with 38 (15.7%) of the patients in the placebo group, Table 4.3. In addition, there were 170 patients (27%) with serious adverse events in study P01:06, who were reported as of the cut-off date of October 1, 2000. The vast majority of these serious adverse events reflected the clinical course of pulmonary arterial hypertension.

Very few serious adverse events were considered related to the administration of the study drug. In the controlled trials (P01:03/04/05) there were 11 patients with possibly or probably attributable serious adverse events in the treprostinil group (4.3%), as compared with 2 (0.8%) on placebo, Tables 4.3 and 4.4.1A.

Table 4.4.1A. Serious Adverse Events Possibly or Reasonably Attributable to the Study Drug in Placebo Controlled Trials with Treprostinil

Adverse Experience	Number (%) of Patients	
	03/04/05 Treprostinil (N=253)	03/04/05 Placebo (N=242)
Vomiting	2 (1)	0 (0)
Heart Failure	1 (<1)	1(<1)
Syncope	1 (<1)	1 (<1)
Dehydration	1 (<1)	0 (0)
Diarrhea	1 (<1)	0 (0)
Hemolytic Anemia	1 (<1)	0 (0)
Headache	1 (<1)	0 (0)
Hemorrhagic Gastritis	1 (<1)	0 (0)
Infusion Site Pain	1 (<1)	0 (0)
Infusion Site Reaction	1 (<1)	0 (0)
Melena	1 (<1)	0 (0)
Neck Pain	1 (<1)	0 (0)
Pain	1 (<1)	0 (0)
Hypotension	1 (<1)	0 (0)
Chest Pain	1 (<1)	0 (0)
Exacerbation of Pulmonary Hypertension	1 (<1)	0 (0)

Many of these events are typical complications of PAH. In particular, the syncopal episodes that were judged as possibly attributable to UT-15 were also judged as due to PAH. Importantly, treprostinil was routinely continued at the same or higher doses in these patients following the event. Given the course of these patients after their events, it is likely that most of these events were related predominantly to the underlying disease. The three cases that are the most likely to have been caused by UT-15 are the hypotension, chest pain, and exacerbation of PAH in patient 02001 that resulted from an overdose of UT-15; the hypotension and hypoxemia that occurred in patient 20002 and resolved with reduction in the dose of UT-15; and the episode of symptomatic hypotension in patient 61007 that was successfully treated with intravenously administered normal saline.

In study P01:06 there were 25 patients (4%) with drug-related serious adverse events, Table 4.3; thus the increased duration of exposure does not appear to increase the incidence of serious adverse events.

Table 4.4.1B. Serious Adverse Events Considered to be Possibly or Reasonably Attributable to Study Drug in Study P01:06

ADVERSE EVENT (PREFERRED TERM)	NUMBER (%) OF PATIENTS
Any Adverse Event	25 (4)
Hypotension	4 (1)
Infusion Site Pain	3 (0)
Hypoxia	3 (0)
Heart Failure	2 (0)
Infusion Site Bleed/Bruise	2 (0)
Nausea	2 (0)
Nausea and Vomiting	2 (0)
Syncope	2 (0)
Confusion	1 (0)
Chest Pain	1 (0)
Dizziness	1 (0)
Dyspnea	1 (0)
Generalized Edema	1 (0)
Headache	1 (0)
Hypochromic Anemia	1 (0)
Infusion Site Infection	1 (0)
Infusion Site Reaction	1 (0)
Kidney Failure	1 (0)
Pruritus	1 (0)
Thrombocytopenia	1 (0)
Vasodilatation	1 (0)
Vomiting	1 (0)

4.4.2 Clinical Events of Special Importance (Deaths, Transplants and Discontinuations Due to Clinical Deterioration)

No patient died in Study P01:03. In Study P01:04/05, there were 9 deaths out of 236 patients in the treprostinil group (3.9%) and 10 deaths in the 233 patients randomized to placebo (4.1%), including deaths that occurred after discontinuation of study drug but within the 12-week study period (Table 3.6.2.3). Three of these deaths in the treprostinil group and three in the placebo group occurred after discontinuation of the study medication.

Of the nine deaths on treprostinil, six were considered related to cardiac decompensation from the underlying disease. The three other patients who died had as their cause of death sepsis following attempted abortion in one patient and catastrophic events related to cardiac catheterization in two patients. None of the deaths were attributed to treatment with treprostinil.

Of 631 patients enrolled in Study P01:06, 36 patients died (5.7%) while receiving treprostinil (on study), and 15 additional deaths occurred within 30 days of discontinuing treprostinil. Typically these deaths were attributed to either to progression of pulmonary hypertension or related cardiovascular events. All deaths were thought to be "not reasonably attributable" to treprostinil.

There were no transplants during Study P01:03 and one transplant on placebo in Study 04/05. There were four transplants during the course of Study P01:06.

Six patients in each of the placebo and treprostinil group in study P01:04/05 had to stop the study medication because of clinical deterioration and thus became candidates for open-label epoprostenol. There were no such patients in study P01:03 and 40 such patients (6%) in study P01:06.

4.5 Special Considerations Regarding Adverse Events

4.5.1 Infusion Site Pain and Its Management

The safety data presented earlier in this section indicate that the major adverse effect of treprostinil therapy is injection site pain or reaction. This adverse event occurs in about 85% of treated patients and is generally related to the rapidity of changes in the infusion rate. Therefore, it characteristically occurs early in treatment when the patient has been started on low doses and may recur or intensify following subsequent dose increments. Injection site pain or reaction is the major reason for limiting dose increments of treprostinil, for initiating dose reductions or for the withdrawal of treatment.

Despite the symptomatic importance of injection site pain or reaction, experience with treprostinil in the treatment of pulmonary arterial hypertension suggests that pain is generally a bothersome but manageable side effect of therapy. In most patients pain can be minimized, substantially controlled or eliminated by careful dose escalation, a reduction in the dose of treprostinil, heat or cold packs, topical medications, common analgesics, anti-inflammatory agents, and infrequently, prescription opioids. Importantly, this localized effect, although discomforting, does not expose patients to any additional risks and does not compromise their overall clinical status. This is apparent from the fact that injection site pain/reaction has frequently been characterized as a severe but not as a serious adverse event. Consequently, the sponsor believes that the severity of this adverse reaction can be fully weighed against the clinical benefits of treatment by both the patient and the physician on a case-by-case basis. This is precisely what happened in the treprostinil trials. In these studies, the proportion of patients discontinuing treatment because of infusion site pain was only 7% of patients in the controlled trials (mean duration 3 months) and only 14% in the open-label study (mean duration 9.6 months).

Nevertheless, the FDA has questioned whether the pain experienced by patients as a result of treatment with treprostinil is so disabling that patients require continuous treatment with narcotic

analgesics to be able to receive the drug. The sponsor has addressed this concern by providing information on three points:

- How were narcotic analgesics prescribed in the controlled trials (P01:03/04/05)?
- How were narcotic analgesics prescribed in the open-label study (P01:06)?
- How were narcotic analgesics actually used during long-term treatment?

In studies P01:04 and P01:05, medications prescribed to treat infusion site pain were captured on a dedicated case report form, which recorded the name and dose of the drug, its route and proposed frequency of use, and start and stop dates. The pain medications were generally prescribed on as "as needed" basis; the case report form did not capture information about actual use. Table 4.5.1A shows the number of patients in the treprostinil treatment group for whom narcotic analgesics were *prescribed* to treat infusion site pain. Approximately one-fourth of patients were given a prescription for a narcotic analgesic; in only 6% was this a schedule II opioid.

Table 4.5.1A Proportion of Treprostinil Patients Who Were Prescribed Narcotic Analgesics to Treat Injection Site Pain in Studies P01:04 and P01:05 (N=236 patients)

	N (%)
All Opioids	64 (27)
Schedule II and III Opioids	45 (19)
Schedule II Opioids	14 (6)

Interestingly, the prescribing of narcotic analgesics to manage injection site pain varied enormously among centers. Of the 35 centers participating in Study P01:04 and P01:05 who had patients on treprostinil, 40% of the centers never prescribed any narcotic analgesics for the management of infusion site pain and 77% never prescribed Schedule II opioids in the patients enrolled in these trials, Table 4.5.1B.

Table 4.5.1B Proportion of Centers That Never Prescribed Narcotic Analgesics to Treat Injection Site Pain in Studies P01:04 and P01:05 (35 centers)

	N (%)
Any Opioids	14 (40)
Any Schedule II and III Opioids	15 (43)
Any Schedule II Opioids	27 (77)

In study P01:06, although the duration of the open-label study was far longer than the duration of the controlled clinical trials (a mean of 9.6 months vs 3.0 months), the prescription of narcotic in the open-label study was not greater and in fact was slightly less than in the controlled trials (Table 4.5.1C).

Table 4.5.1C. Proportion of Patients Who Were Prescribed Narcotic Analgesics to Treat Injection Site Pain At Any Time in Study P01:06 (N=631 patients)

	N (%)
All Opioids	135 (21)
Schedule II and III Opioids	97 (15)
Schedule II Opioids	30 (5)

As in Studies P01:04 and P01:05, the prescribing of narcotic analgesics in study P01:06 varied greatly among centers. Approximately 34% of centers did not prescribe opioids to manage infusion site pain, and most centers (71%) did not prescribe Schedule II opioids.

Tables 4.5.1B and 4.5.1C show data about the prescribing but not the actual use of narcotics. To address actual use, the sponsor (following discussion with the FDA) undertook an effort to quantify the actual use of narcotic analgesics by patients receiving treprostinil. Accordingly, all centers participating in study P01:06 were asked to contact each of the 545 patients still on treatment and to ask about their use of opioids on the day prior to being contacted. [This provides a "snapshot" of the actual use of opioids at a fixed time.] Contact was successfully made in 535 of the 545 patients (98%). As shown in Table 4.5.1D., the frequency of use of narcotic analgesics was low (only 8%), and in particular, the frequency of use of Schedule II opioids was extremely low (only 1%).

Table 4.5.1D. Actual Use of Narcotic Analgesics in Patients Receiving Treprostinil on Day Prior to Contact (N=535 patients)

	N (%)
All Opioids	45 (8)
Schedule II & III Opioids	30 (6)
Schedule II Opioids	7 (1)

In conclusion, although narcotic analgesics are sometimes prescribed to treat injection site pain in patients receiving treprostinil, such practice largely reflects the prescribing preferences of the patient's physician. Some patients receive opioids prophylactically; others receive these drugs intermittently; very few receive these drugs on a daily basis; and some patients never receive opioids to manage injection site pain.

4.6 Overdose

Fifteen patients experienced an overdose of treprostinil during the clinical development program. The most common error leading to overdose was an accidental bolus administration (n = 6) while flushing the infusion line after inserting it subcutaneously. The next most common errors were incorrectly setting the program for the infusion pump (n= 3) or changing the concentration of the infusate without changing the infusion rate (n=2). In addition, in three cases, treprostinil was erroneously supplied to patients who had been on placebo. One other case is unexplained, but possibly was an error by the site staff. This patient, the very first to enter Study P01:03, had a six-fold higher plasma

concentration than expected and had a marked hypotensive response. In each case in which an excess treprostinil led to an adverse event, the event was non-serious and the patient recovered quickly after infusion was interrupted or restored to the correct rate.

In 13 of these 15 patients the overdose caused adverse effects (Table 4.6), all characteristic of prostaglandin treatment. Among the remaining two patients, one patient did not experience any adverse effect and in the other, the dose and symptoms could not be discerned from the case report form.

Table 4.6. Adverse Events During Overdosing with Treprostinil

Adverse Event	Number of Events
Nausea	6
Headache	5
Vomiting	3
Flushing	3
Dizziness/Near Syncope	3
Hypotension	2
Diarrhea	2
Body Pain	2
Infusion Site Pain/reaction	2

Interestingly, systemic events predominate over local site reactions during acute overdose of the drug. Nausea, headache, diarrhea, vomiting, and various body pains lasting several hours are the typical presentations. Dizziness, near syncope and hypotension are more commonly noted after overdose than during slow uptitration of the drug. These cases were self-limited and could be managed by withholding the infusion for several hours until symptoms of drug excess resolved.

4.7 Conversion of Epoprostenol to Treprostinil

In **Study P01:11** patients who were receiving but requiring withdrawal of treatment with intravenous epoprostenol were offered treatment with subcutaneous treprostinil. Typical reasons included severe or recurrent infusion line complications (especially sepsis) or severe pain. Treprostinil was to be initiated at a dose not to exceed one-half the current dose of intravenous epoprostenol. The dose of treprostinil was to be maintained at least six hours, during which time the dose of epoprostenol was to be adjusted downward slowly, in no more than 2 ng/kg/min amounts. After at least six hours, the dose of treprostinil was increased by a maximum of one-half of the initial treprostinil dose and epoprostenol was simultaneously titrated downward. This process was continued until epoprostenol was discontinued and the patient was stable on treprostinil. Systemic dose-limiting adverse experiences were first managed with reduction in the dose or discontinuation of epoprostenol, but the dose of treprostinil could be reduced, if necessary.

As of May 1, 2001, eight patients (6 men, 2 women; age range 29-54) have been safely withdrawn from intravenous epoprostenol and transitioned to subcutaneous treprostinil, Table 4.7. Patients had a variety of pulmonary hypertension etiologies including primary pulmonary hypertension (n=5), connective tissue disease (n=1), congenital heart disease (n=1), and HIV infection (n=1). Prior to the transition, all patients had improved symptoms with epoprostenol therapy and were clinically stable, except patient 1153002 whose pulmonary hypertension was reported as worsening at the time of transition. The highest epoprostenol dose at initiation of transition to treprostinil was 75 ng/kg/min.

Table 4.7 Summary of Study P01:11 (Epoprostenol to Treprostinil conversion study)

Patient Number	Reason for epoprostenol withdrawal	Time on epoprostenol prior to transition (months)	Epoprostenol dose at initiation of transition (ng/kg/min)	Treprostinil dose at completion of transition (ng/kg/min)	Time to transition (hours)	Time on treprostinil (months)
1102001	Recurrent paradoxical emboli	5	3.5	3	24	15
1121001	Central line infections	29	26	15	50	5
1121002	Jaw/leg pain, line infections	36	75	65	120	3
1129001	Line infections & septicemia	26	22.5	23.3	42	2
1129002	Line infections, epidermal necrosis	33	40	36.6	54	2
1153001	Line infections	21	15	7	36	9
1153002	Severe headache, jaw pain & diarrhea	30	13	10	22	6
1153003	Line infections & septicemia	19	18	16	22	5

Doses of treprostinil at the completion of the transition were approximately equal to the doses of epoprostenol immediately prior to withdrawal. The period of transition to treprostinil ranged from 1 to 5 days. Doses of treprostinil were increased in 1 to 10 ng/kg/min increments while doses of epoprostenol were reduced by 2 to 10 ng/kg/min decrements.

During transition, adverse events were infrequent, were typical of excess prostacyclin (including headache, flushing and restlessness) and were readily managed with reduction or discontinuation of epoprostenol. Patients also reported mild-to-moderate treprostinil infusion site reactions. No exacerbation of symptoms of pulmonary hypertension was observed during the transition. No serious adverse events attributable to discontinuation of epoprostenol or initiation of treprostinil were reported in any patient.

Patient 1102001 experienced a serious cerebral vascular accident, which the investigator attributed to the central venous catheter used to infuse epoprostenol; this patient was being transitioned from epoprostenol to treprostinil due to recurrent paradoxical cerebral emboli.

All eight patients are alive; seven remain stable on treprostinil. One patient (1153002) experienced worsening pulmonary hypertension with epoprostenol therapy and continues to have worsening symptoms with treprostinil.

4.8 Conclusions Regarding Safety

The results of two identical double-blind randomized controlled trials and an open-label follow-up study have shown that treprostinil is predictably accompanied by injection site pain or reactions. However, treatment with treprostinil is not characterized by the serious and potentially life-threatening side effects that can accompany the use of intravenous epoprostenol — the only drug presently approved for the treatment of pulmonary arterial hypertension.

The following summarizes our present knowledge about the occurrence of injection site pain or reaction with treprostinil.

- This adverse event occurs in about 85% of treated patients and is generally related to the rapidity of changes in the infusion rate. Therefore, it characteristically occurs early in treatment when the patient has been started on low doses and may recur or intensify following subsequent dose increments.

- Injection site pain or reaction is the most common reason for being unable to increase the dose of treprostinil, for reduction in dose, or for the withdrawal of treatment.

- In general, infusion site pain can be substantially controlled or eliminated by careful dose escalation, a reduction in the dose of treprostinil, change in the infusion site, heat or cold packs, topical medications, common analgesics, anti-inflammatory agents, and infrequently, prescription opioids.

- The incidence of adverse events decreases with increasing duration of exposure. This was particularly true of localized events (infusion site pain and reaction), but it was also valid for systemic events (e.g., diarrhea, headache, nausea).

- In clinical trials control of injection site pain has been sufficiently successful such that less than 10% of treated patients in 8-12 week controlled trials and less than 15% of treated patients in long-term open-label studies have found the severity of pain to outweigh the clinical benefits produced by treatment.

Other adverse events that were more common in patients receiving treprostinil than those treated with placebo include headache, diarrhea and nausea, jaw pain, vasodilatation, edema and anorexia. All of these have been identified as characteristic adverse effects of prostaglandin therapy in earlier studies.

There were no clinically meaningful changes in vital signs, in electrocardiographic intervals, in clinical chemistry or hematology indices, or in INR values seen in treprostinil-treated patients in placebo-controlled or open-label studies. Moreover, the general adverse event profile characterized in placebo-controlled studies remained remarkably consistent with more prolonged exposure.

5 BENEFIT-TO-RISK CONSIDERATION FOR THE USE OF TREPROSTINIL FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

5.1 Limitations of Existing Therapy

Pulmonary arterial hypertension is a rare but serious disorder with very limited therapeutic options. At present only one drug (epoprostenol) is approved for the treatment of pulmonary arterial hypertension, but use of epoprostenol requires implantation of an indwelling intravenous line, and short- and long-term use of such lines is associated with clinically significant risk of complications, which include:

- risk of trauma and pneumothorax with catheter placement
- risk of local site infection from the catheter
- risk of sepsis from the catheter
- risk of thrombosis of the catheter
- risk of dislodgment or perforation of the catheter
- risk of stroke (due to paradoxic embolus) from the catheter
- risk of cardiovascular collapse from interruption of the infusion
- risk of cardiovascular collapse from infusion pump malfunction

Approximately 14% of patients evaluated in long-term trials with epoprostenol developed sepsis (some reported more than one episode), which occurred at a rate of 0.32 infections per patient per year. In addition, 14-21% developed local infections related to the delivery system. These complications constitute established risks of an indwelling catheter and are unavoidable. Occlusion, dislodgement and other mechanical and technical difficulties with the indwelling catheters are also frequent occurrences, the majority of which lead to serious adverse reactions. Among the most serious of these complications are malfunctions of the catheter or the infusion pump that result in sudden cessation of the infusion of epoprostenol. Because epoprostenol has a very short duration of action (approximately 1-2 minutes), sudden termination of the infusion not only leads to a loss of efficacy but also to rebound pulmonary hypertension, which becomes manifest as cardiovascular collapse.

During the development of epoprostenol, the potential of such serious adverse consequences was deemed so important that patients with only mild symptoms of pulmonary hypertension (class II patients) were excluded from clinical trials with the drug. Current labelling for epoprostenol continues to exclude class II patients because of these risks. Fortunately, because of its longer half-life (approximately 3-4 hours) and subcutaneous route of delivery, the administration of treprostinil has not been complicated by sepsis during long-term use or by cardiovascular collapse following the abrupt cessation of treatment.

The potential for life-threatening complications is sufficiently well recognized that many patients who might otherwise be candidates for epoprostenol do not receive treatment with the drug. This may occur because they have experienced an adverse effect from the drug or from its delivery system or do not wish to subject themselves to the considerable inconvenience and serious risks of treatment. At the present time, there is no effective treatment for such patients. For such individuals, treprostinil represents an alternative way of receiving effective prostanoid therapy, thereby addressing an important unmet need.

5.2 Ability of Treprostinil to Fulfill Unmet Need

In considering the approval of epoprostenol for the treatment of pulmonary arterial hypertension, the FDA relied on changes in 6-minute walk distance, symptoms of pulmonary hypertension, the dyspnea-fatigue rating and hemodynamic variables in reaching a favorable decision on the drug. Epoprostenol was approved, even though the data with the drug were collected in an open-label manner without a placebo control as the drug required implantation and maintenance of an indwelling central venous catheter for continuous infusion, which carried its own risks. Given the unmet need for an effective treatment for patients with pulmonary arterial hypertension, the FDA concluded that the ratio of benefit to risk was in the patients' favor. United Therapeutics is well aware of the complexity of this decision, since we were the team that developed epoprostenol for the treatment of pulmonary arterial hypertension for our former employer (Burroughs Wellcome, now GlaxoSmithKline).

Despite the approval and availability of epoprostenol, there still remains an unmet need for a safe and effective treatment for patients with pulmonary arterial hypertension who cannot tolerate epoprostenol or its delivery system or who do not wish to have or to care for an indwelling intravenous line. The data collected in three controlled trials with treprostinil strongly support the hypothesis that the drug is an effective approach to the treatment of this disease, which is free of the life-threatening risks associated with continuous intravenous therapy. Treprostinil has been shown to improve all of the efficacy measures that were favorably affected by epoprostenol in its trials. Yet, it should be noted that the efficacy of treprostinil has been demonstrated in double-blind placebo controlled trials, whereas epoprostenol was evaluated only in open-label studies where no placebo was administered. The consistency of the benefits of treprostinil was apparent across the three trials carried out with the drug and across all clinically relevant variables measured in the studies.

The sponsor understands that, in its review of treprostinil, the FDA believes that the effects of treprostinil seen in its controlled trials were of smaller magnitude than the effects of epoprostenol seen in its controlled trials. The sponsor would suggest, however, that any comparison of the magnitude of effect of different treatments in different trials is always inherently suspect and should be carried out with great caution (if ever). This is particularly true if one drug has been evaluated in double-blind studies

(treprostinil) and the other drug has been evaluated in open-label studies without a placebo control (epoprostenol). Drug effects in open-label studies are always larger than those in double-blind trials. Comparisons of treprostinil and epoprostenol are further complicated by the fact that the trials with epoprostenol (but not those with treprostinil) excluded patients with class II symptoms, which tend to show the smallest response to drug treatment.

Furthermore, in the sponsor's view, it is inadequate to characterize the magnitude of the treatment effect of treprostinil by focusing on a single isolated measure of efficacy, i.e., the distance traversed during a 6-minute walk test. Instead, it is more useful to consider the totality of data (including the symptoms experienced by the patient during the conduct of the test). The following paragraphs summarize the key points regarding efficacy:

- When both distance and symptoms were considered together as important components of functional capacity, patients in the treprostinil group exercised further with fewer symptoms than patients in the placebo group.

- When compared with placebo, patients treated with treprostinil were more likely to have pre-existing symptoms resolve completely and were less likely to have symptoms develop for the first time. This was true across a broad range of symptoms, including those that constituted objective events (e.g., syncope) rather than simply subjective impressions (e.g., palpitations).

- Treprostinil produced improvements in the physician-based dyspnea-fatigue rating and the patient-based physical domain of the Minnesota quality of life instrument.

- Treprostinil was associated with sustained hemodynamic benefits that are characteristic of those believed to be required for successful treatment of pulmonary arterial hypertension.

These benefits were observed in an investigative environment that was specifically designed to minimize bias, i.e., unlike earlier studies in pulmonary arterial hypertension, the studies were double-blind and utilized independent assessors of exercise performance.

Therefore, one can conclude that the spectrum of benefits seen with treprostinil are qualitatively identical to those seen with epoprostenol — with one possible exception. In one trial with epoprostenol which enrolled a total of 81 patients, there were fewer deaths in patients treated with epoprostenol than in those assigned to the control group (0 deaths in epoprostenol group vs. 8 deaths in the control group, nominal $P < 0.05$). Such a dramatic difference in mortality rates was not observed in trials with treprostinil. However, the mortality finding with epoprostenol can hardly be considered robust, given the small number of patients and events and given a greater severity of illness before randomization in the patients assigned to the control group. It is not likely that — if

epoprostenol were evaluated in another trial of 81 patients or in a much larger study — that a survival benefit would be observed. Indeed, little difference in mortality was observed with epoprostenol in a second (and larger) controlled trial of patients with pulmonary arterial hypertension (secondary to scleroderma) carried out following initial approval of the drug.

Even if one were to believe that the magnitude of the benefits of treprostinil was smaller than that of epoprostenol, the relation of benefit to risk is nevertheless likely to be more favorable with treprostinil than with epoprostenol. Based on the observations in trials with both drugs, epoprostenol's larger postulated effect (if present) would need to be considered in relation to the greater rigors and substantiated risks associated with use of the intravenous drug. For patients who can tolerate and are willing to accept such risks, epoprostenol can be an excellent choice. For patients who cannot or will not tolerate such risks, treprostinil represents an excellent alternative.

5.3 Relation of Benefit to Risk

Given the benefits of treprostinil, what risks should be considered in reaching a conclusion about the relation of benefit to risk?

Treatment with treprostinil is frequently accompanied by injection site pain or reactions, which may be bothersome and require active management. However, this localized effect, although discomforting, does not expose patients to any additional risks and does not compromise their overall clinical status. The severity of this adverse reaction can be fully weighed against the clinical benefits of treatment by both the patient and the physician on a case-by-case basis.

This is precisely what happened in the treprostinil trials. In these studies, the proportion of patients discontinuing treatment with treprostinil because of pain is low, i.e., only 7% of patients in the controlled trials (mean duration 2-3 months) and only 14% in the open-label study (mean duration 9.6 months). These low withdrawal rates indicate that most patients viewed the symptomatic benefit as more meaningful than the discomfort they experienced.

Although narcotic analgesics are sometimes prescribed to treat injection site pain in patients receiving treprostinil, such practice largely reflects the prescribing preferences of the patient's physician. Some patients are prescribed opioids prophylactically, and others receive these drugs intermittently; very few use these drugs on a daily basis.

As a result, the subcutaneous administration of treprostinil therapy produced favorable and clinically relevant effects in patients with pulmonary arterial hypertension and can be expected to improve the lives of many patients with symptoms of the disease. The clinical benefits of treprostinil are not negated by any apparent risk, including the occurrence of infusion site pain and reaction.

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Appendix A: Remodulin™ Draft Package Insert

NDA 21-272

PRODUCT INFORMATION

REMODULIN ā (treprostinil sodium)
Injection

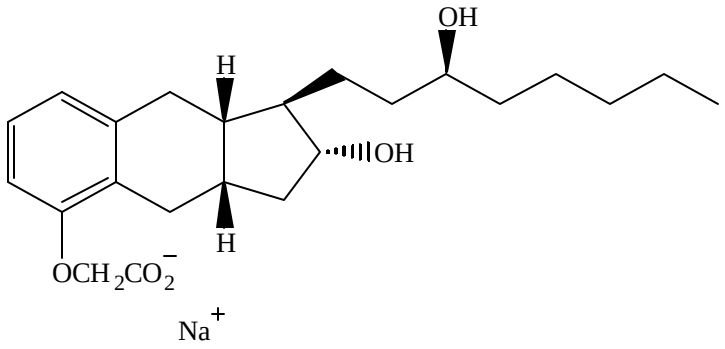
(a) Description

Remodulin (treprostinil sodium) Injection is a sterile sodium salt formulated for subcutaneous administration. Remodulin is supplied in 20 mL multi-use vials in four strengths, containing 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL or 10.0 mg/mL of treprostinil. Each mL also contains 5.3 mg sodium chloride (except for the 10.0 mg/mL strength which contains 4.0 mg sodium chloride), 3.0 mg metacresol, and 6.3 mg sodium citrate. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Treprostinil is a tricyclic benzindene analogue of epoprostenol (prostacyclin, PGI_2) with potent pulmonary and systemic vasodilatory activity. Treprostinil is a potent inhibitor of platelet aggregation *in vitro* and *in vivo*. Treprostinil is chemically stable at room temperature and neutral pH.

Treprostinil is (1R,2R,3aS,9aS)-[[2,3,3a,4,9,9a-Hexahydro-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H-benz[f]inden-5-yl]oxy]acetic acid monosodium salt. Treprostinil sodium has a molecular weight of 412.49 and a molecular formula of $C_{23}H_{33}NaO_5$.

The structural formula of treprostinil is:



(b) Clinical Pharmacology

General: The major pharmacological actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds, and inhibition of platelet aggregation. In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. The effect of treprostinil on heart rate in animals varies with dose. No major effects on cardiac conduction have been observed.

(1) Pharmacokinetics:

In humans, following the initiation of subcutaneous infusion of Remodulin, steady-state plasma concentrations are usually achieved within 15 to 18 hours. Steady-state plasma concentrations of treprostinil are dose-proportional at subcutaneous infusion rates of 2.5 to 15 ng/kg/min; however, it is not known if the proportionality between dose and steady-state plasma levels is maintained at

infusion rates greater than 15 ng/kg/min. REMODULIN when administered chronically as a subcutaneous infusion is completely absorbed and has a mean apparent elimination half-life of 3 hours compared to 45 minutes when administered intravenously. The mean volume of distribution and plasma clearance for treprostinil are 1.1 L/kg and 589 mL/kg/hr, respectively.

In a [^{14}C] treprostinil mass balance and metabolic fate study in healthy volunteers, 78.6% and 13.4% of the subcutaneous radioactive dose were recovered in the urine and feces, respectively, over a period of 224 hours. There was no single major metabolite observed. Five metabolites were detected in the urine, ranging from 10.2% to 15.5%. of the dose administered These five metabolites accounted for a combined total of 64.4%. Three are products of oxidation of the 3-hydroxyloctyl side chain, one is glucuronide conjugate (treprostinil glucuronide) and one is unidentified. Only 3.7% of the dose was recovered in the urine as unchanged parent drug.

In a chronic pharmacokinetic study in normal volunteers with chronic subcutaneous Remodulin doses ranging from 2.5 to 15 ng/kg/min, steady state plasma treprostinil concentrations achieved peak levels twice (at 1 a.m. and 10 a.m., respectively) and achieved trough levels twice (at 7 a.m. and 4 p.m., respectively). The peak concentrations were ~20% to 30% higher than trough concentrations. Dose adjustments are not deemed to be necessary due to diurnal variation.

(2) Special Populations:

Hepatic Insufficiency: An acute study of Remodulin™ administered subcutaneously at a dose of 10 ng/kg/min for 150 minutes was conducted in nine patients with portopulmonary hypertension and stable, mild or moderate hepatic dysfunction. Remodulin was well tolerated and improved cardiopulmonary hemodynamics. Hepatic dysfunction reduced plasma clearance of Remodulin by up to 80% compared to healthy adult volunteers primarily by lowering the volume of distribution without effecting plasma half-life. Remodulin should be increased more conservatively in patients with hepatic dysfunction and these patients should be closely monitored for signs and symptoms or emergence of AEs due to excess Remodulin.

Renal Insufficiency: No studies have been performed in patients with renal impairment. Treprostinil is not excreted to any significant degree by the kidney; however, patients with renal impairment may have different sensitivities (usually increased sensitivity) to agents. Based on the individual patient dose titration recommended for Remodulin, doses of Remodulin should be increased more conservatively in patients with renal insufficiency.

Obese Patients: Obese subjects (BMI greater than 30.0 kg/m^2) clear treprostinil at a slower rate. Since doses of Remodulin are increased from very low initial doses to doses that improve disease symptoms while minimizing adverse effects, dosing to ideal body weight in obese patients should not be necessary.

Clinical Trials in Pulmonary Arterial Hypertension (PAH):

Hemodynamic Effects: Acute infusion of Remodulin at 10 ng/kg/min intravenously for 75 minutes followed by a 10 ng/kg/min infusion subcutaneously for 150 minutes, in patients with primary pulmonary hypertension produced increases in cardiac index (CI) and mixed venous oxygen saturation (SvO_2), and decreases in mean pulmonary arterial pressure (PAPm) , mean right atrial pressure (RAPm) and pulmonary vascular resistance indexed (PVRI), with little effect on mean systemic arterial pressure (SAPm) or heart rate (HR).

Chronic continuous, subcutaneous infusion of Remodulin in NYHA Class II, III or IV patients with PAH was studied in two identical, 12-week, double-blind, placebo-controlled, multicenter, parallel-

group, randomized trials comparing Remodulin plus conventional therapy to conventional therapy alone. Dosage of Remodulin was determined as described in DOSAGE AND ADMINSTRATION and averaged 9.3 ng/kg/min at Week 12. Conventional therapy used to treat patients with PAH included some or all of the following: anticoagulants, oral vasodilators, diuretics, digoxin, and oxygen.

As the two studies were identical in design and conducted simultaneously, results were analyzed both pooled and individually. As shown in Table 1, hemodynamic effects after chronic therapy with Remodulin™ were generally consistent with the pharmacological effects seen acutely. There were statistically significant increases in CI and SvO_2, and statistically significant decreases in PAPm, RAPm, PVRI and SVRI in patients treated with Remodulin for 12 weeks compared to patients treated with placebo. Heart rate and SAPm were unchanged. In patients with pulmonary hypertension, elevated RAPm and PAPm, and reduced CO and SvO_2 are predictive of mortality.

Table 1: Hemodynamics During Chronic Administration of Remodulin in Patients with PAH

Hemodynamic Parameter	Baseline		Mean change from baseline at Week 12	
	Remodulin (N=204-231)	Placebo (N=215-235)	Remodulin (N=163-199)	Placebo (N=182-215)
CI ($L/min/m^2$)	2.37 ± 0.06	2.24 ± 0.05	+0.12 ± 0.04*	-0.06 ± 0.04
PAPm (mmHg)	61.8 ± 1.16	59.9 ± 0.96	-2.3 ± 0.51*	+0.7 ± 0.58
RAP (mmHg)	10.3 ± 0.38	10.0 ± 0.39	-0.5 ± 0.36*	+1.4 ± 0.33
PVRI ($mmHg/L/min/m^2$)	26.51 ± 0.97	25.11 ± 0.87	-3.54 ± 0.64*	+1.20 ± 0.57
SVRI ($mmHg/L/min/m^2$)	37.87 ± 1.05	39.23 ± 1.02	-3.54 ± 0.96*	-0.80 ± 0.85
SvO_2 (%)	61.5 ± 0.70	60.2 ± 0.77	+2.0 ± 0.76*	-1.4 ± 0.65
SAPm (mm Hg)	89.6 ± 0.92	90.7 ± 0.89	-1.7 ± 0.86	-1.0 ± 0.91
HR (bpm)	82.4 ± 0.83	82.1 ± 0.97	--0.5 ± 0.80	-0.8 ± 0.74

*Denotes statistically significant difference between Remodulin and placebo, $p \leq 0.0005$
CI = cardiac index; PAPm = mean pulmonary arterial pressure; PVRI = pulmonary vascular pressure indexed; RAPm = mean right atrial pressure, SAPm = mean systemic arterial pressure; SVRI = systemic vascular resistance indexed; SvO_2 = mixed venous oxygen saturation, HR = heart rate

Clinical Effects: Exercise capacity, as measured by the six-minute walk test, improved significantly in patients receiving continuous subcutaneous Remodulin plus conventional therapy (N=232) for 12 weeks compared to those receiving conventional therapy plus placebo (N=236) (p=0.0064).

Improvements were apparent as early as Week 6 of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by the Dyspnea-Fatigue Rating and Borg Scale. Signs and symptoms of PAH and Quality of Life also improved.

(c) Indications and Usage

Remodulin™ is indicated for the long-term subcutaneous treatment of Pulmonary Arterial Hypertension in NYHA Class II, III, and IV patients. (see Clinical Pharmacology: Clinical Trials).

(d) Contraindications

Remodulin in contraindicated in patients with known hypersensitivity to the drug or to structurally related compounds

(e) Warnings

Remodulin has been administered intravenously in acute clinical trials with no unexpected adverse effects. However, no chronic controlled trials have been performed with intravenous Remodulin therefore it is indicated for subcutaneous use only.

(f) Precautions

(1) General

Remodulin should be used only by clinicians experienced in the diagnosis and treatment of PAH.

Remodulin is a potent pulmonary and systemic vasodilator. Initiation of Remodulin must be performed in a setting with adequate personnel and equipment for physiologic monitoring and emergency care. Dosage adjustments in clinical trials were based on the patient's signs and symptoms of PAH and side effects of Remodulin. Dosage of Remodulin should be adjusted at the first sign of recurrence or worsening of symptoms attributable to PAH or the occurrence of intolerable adverse events associated with Remodulin. (see DOSAGE and ADMINISTRATION)

The decision to initiate therapy with Remodulin should be based on the understanding that there is a high likelihood that subcutaneous therapy with Remodulin will be needed for prolonged periods, possibly years, and the patient's ability to administer Remodulin and care for an infusion system should be carefully considered. As with any potent vasodilator, abrupt withdrawal or sudden large reductions in dosage of Remodulin may result in worsening of PAH symptoms. In clinical trials, no patient death from discontinuation of Remodulin was judged attributable to the interruption of Remodulin. Only three of 55 (5%) patients with abrupt disruption of Remodulin developed increased symptoms of PAH, and no patients developed hemodynamic instability. In addition, among patients who discontinued Remodulin abruptly, no relationship has been established between abrupt discontinuation and rebound pulmonary hypertension.

(2) Information for patients

Patients receiving Remodulin should be given the following information: Remodulin is infused continuously through a subcutaneous catheter, via an infusion pump. The decision to receive Remodulin should be based upon the understanding that therapy with Remodulin will be needed for prolonged periods, possibly years, and the patients ability to accept, place and care for a subcutaneous catheter and to use an infusion pump should be carefully considered. Additionally, patients should be aware that subsequent disease management may require the initiation of an intravenous therapy.

(3) Drug interactions

Additional reductions in blood pressure may occur when Remodulin™ is administered with diuretics, anthihypertensive agents, or other vasodilators. When other antiplatelet agents or anticoagulants are used concomitantly, there is the potential for Remodulin to increase the risk of bleeding. However, patients receiving Remodulin in clinical trials were maintained on anticoagulants without evidence of increased bleeding. No untoward clinical manifestations have been observed in patients in whom Remodulin was used concurrently with the following classes of drugs: anticoagulants, diuretics, cardiac glycosides, calcium channel blockers, analgesics, antipyretics, nonsteroidal anti-inflammatories, opioids, corticosteroids, and other medications. Chronic subcutaneous Remodulin administration required concomitant therapies to manage adverse events associated with the use of Remodulin. Adverse events associate with these concomitant therapies may occur and should be handled as medically appropriate.

Effect of Other Drugs on Treprostinil

The effect of large daily doses of acetaminophen (4g/day) on the kinetics of treprostinil was investigated in a healthy volunteer study. The results demonstrate that acetaminophen does not have any clinically important effect on the pharmacokinetics of treprostinil. Treprostinil did not significantly affect the plasma protein binding of digoxin or warfarin when evaluated in human plasma at physiologic concentrations. In a multivariate analysis of treprostinil plasma clearance values obtained in two controlled trials, 6% of the variability in treprostinil plasma clearance values could be explained by the presence of furosemide (both treprostinil and furosemide undergo glucoronidation at the carboxylate group during metabolism). Based on the modest suggestion of an interaction, a reduction in dose in patients receiving furosemide is not recommended, although patients should be monitored for excess adverse effects of Remodulin.

Effect of Treprostinil on Other Drugs
***In Vitro* Studies**

Results from an *in vitro* study in human hepatic microsomes demonstrated that treprostinil does not significantly inhibit the following P450 isoforms - CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. In a separate study which investigated the induction effect of treprostinil on rat liver microsomal cytochrome P450 enzymes, treprostinil was found to lack any significant induction effect on (CYP1A), (CYP2B) and (CYP3A).

In Vivo Studies

Treprostinil had no effect on warfarin pharmacodynamics as measured by the effect on INR. Treprostinil also had no effect on the pharmacokinetics of either the R- or S-enantiomer of warfarin.

(4) Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies have not been performed to evaluate carcinogenic potential. *In vitro* and *in vivo* mutagenicity studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil was not teratogenic in pregnant rats at doses up to 900 ng/kg/min. No developmental toxicity was seen in rabbits at 50 ng/kg/min. In reproductive performance studies in rats, treprostinil had no effect on male on female fertility at doses up to 450 ng/kg/min.

(5) Pregnancy

Pregnancy Category B. No developmental toxicity was seen in rats at any dose of treprostinil up to 900 ng/kg/min and in rabbits at 50 ng/kg/min. In pregnant rabbits, developmental toxicity characterized by minimal increases in fetal skeletal variations per litter was observed at doses of 150 and 300 ng/kg/min and was associated with maternal toxicity. There are no adequate and well-controlled studies in pregnant women. Remodulin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

(6) Nursing mothers

It is not known whether treprostinil is excreted in human milk or absorbed systemically after ingestion. Because many drugs are excreted in human milk, caution should be exercised when Remodulin™ is administered to nursing women.

(7) Pediatric use

Safety and effectiveness in pediatric patients have not been established. Clinical studies of Remodulin did not include sufficient numbers of patients aged ≤16 years to determine whether they respond differently from older patients. In general, dose selection should be cautious.

(8) Geriatric use

Clinical studies of Remodulin did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant disease or other drug therapy.

(g) Adverse Reactions

Interpretation of AEs reported during clinical trials should be undertaken with an awareness of expected events attributable to the progression of the underlying disease, to Remodulin, and/or to the drug delivery system.

Interpretation of adverse events is complicated by the clinical features of PAH, which are similar to some of the pharmacological effects of Remodulin (e.g., dizziness, syncope). Adverse events probably related to the underlying disease include dyspnea, fatigue, chest pain, right ventricular heart failure, and pallor. Several adverse events can clearly be attributed to Remodulin, the most common of which is pain at the infusion site, tolerated by a majority of patients. Other adverse events include infusion site reaction, diarrhea, jaw pain, edema, vasodilatation and nausea. Infusion site reaction was defined as any local adverse event other than infusion site pain or infusion site bleeding/bruising, such as erythema, induration, or rash.

Adverse Events During Chronic Dosing: In an effort to separate the adverse effects of Remodulin™ from those of the underlying disease, Table 2 lists adverse events that occurred at a rate at least 5% more frequently in patients treated with Remodulin than with placebo in controlled trials in PAH.

Table 2: Frequency of Adverse Events Regardless of Attribution Occurring in Patients with PAH with ≥5% Difference Between Remodulin and Placebo in Controlled Studies

Adverse Event	UT- (N=236) N (%)	Placebo (N=233) N (%)
Occurrence More Common with **Remodulin**		
General (Body as Whole)		
Jaw pain	31 (13.1)	11 (4.7)
Gastrointestinal (Digestive)		
Diarrhea	58 (24.6)	36 (15.5)
Metabolic and Nutritional		
Edema	21 (8.9)	6 (2.6)
Neurological/Nervous		
Vasodilatation	25 (10.6)	11 (4.7)
Skin and Appendages		
Infusion site pain	200 (84.7)	62 (26.6)
Infusion site reaction	196 (83.1)	62 (26.6)
Occurrence More Common with Placebo		
Hematologic and Lymphatic		
Ecchymosis	9 (3.8)	27 (11.6)
Respiratory		
Cough	7 (3.0)	19 (8.2)
Skin and Appendages		
Infusion site bleed/bruise	79 (33.5)	102 (43.8)

Table 3 lists all adverse events reported in controlled clinical trials of patients with PAH, that were significantly more frequently encountered in the Remodulin™ group than in the placebo group, regardless of attribution.

Table 3: AEs That Were Significantly (p<0.1) More Frequently Encountered in the Remodulin Group Than in the Placebo Group, Regardless of Attributability

AE Description, as COSTART Preferred Term	Number of events Remodulin-group / placebo group	p-value
Any AE	231 / 218	0.0173
Infusion site pain	200 / 62	<0.0001
Infusion site reaction	196 / 62	<0.0001
Diarrhea	58 / 36	0.0091
Jaw pain	31 / 11	0.0010
Vasodilatation	25 / 11	0.0127
Edema	21 / 6	0.0026
Anorexia	11 / 4	0.0592
Epistaxis	10 / 4	0.0904
Nausea and vomiting	7 / 2	0.0909
Hypokalemia	5 / 0	0.0316
Melena	5 / 0	0.0316

Adverse Events Attributable to the Drug Delivery System in PAH Controlled Trials: There were no reports of infection related to the drug delivery system. There were 187 infusion system complications reported in 28% of patients (23% Remodulin, 33% placebo); 173 (93%) were pump related and 14 (7%) related to the infusion set. Eight of these patients (4 Remodulin, 4 placebo) reported non-serious adverse events resulting in infusion system complications. Adverse events resulting from problems with the delivery system did not lead to clinical instability or rapid deterioration, although in some cases PAH symptoms reappeared.

(h) Overdosage

Signs and symptoms of overdose with Remodulin during clinical trials are similar to expected dose-limiting pharmacological effects of Remodulin, including flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin.

In controlled clinical trials, seven patients received some level of overdose and in the chronic, uncontrolled trial seven additional patients received an overdose; these occurrences resulted from accidental bolus of Remodulin, errors in pump programmed rate of administration and prescription of incorrect dose. In only two cases did excess delivery of Remodulin produce an event of substantial hemodynamic concern (hypotension, near-syncope). No deaths occurred as a result of overdose.

(i) Dosage and Administration

Remodulin™ is supplied in 20 mL vials in concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL and 10.0 mg/mL.

Initial Dose:

Remodulin is administered by continuous subcutaneous infusion. The infusion rate is initiated at 1.25 ng/kg/min. If this initial dose cannot be tolerated, the infusion rate should be reduced to 0.625 ng/kg/min.

Dosage Adjustments:

The goal of chronic dosage adjustments is to establish a dose at which PAH symptoms are improved, while achieving an acceptable side effect profile. The infusion rate should be adjusted based on PAH signs and symptoms and Remodulin side effects. The infusion rate should be increased in increments of no more than 1.25 ng/kg/min per week for the first four weeks and then no more than 2.5 ng/kg/min per week for the remaining duration of infusion. Dose-related symptoms may necessitate a decrease in infusion rate; however, the event may resolve without dosage adjustment. Should an adverse event worsen and/or become intolerable, the infusion rate should be reduced.

Administration:

Remodulin is administered by continuous subcutaneous infusion, via a self-inserted subcutaneous catheter, using a infusion pump designed for subcutaneous drug delivery. To avoid potential interruptions in drug delivery, the patient should have access to a backup infusion pump and subcutaneous infusion sets. The ambulatory infusion pump used to administer Remodulin should: (1) be small and lightweight, (2) be able to adjust infusion rates in approximately 0.002 mL/hr, (3) have occlusion/no delivery, low battery, programming error and motor malfunction alarms, (4) have delivery accuracy of ±6% or better and (5) be positive pressure driven. The reservoir should be made of polyvinyl chloride, polypropylene or glass.

Infusion rates are calculated using the following formula.

Infusion Rate (mL/hr) **= Dose** (ng/kg/min) **x Weight** (kg) **x [0.00006/Remodulin concentration** (mg/mL)**]**

Tables 4 through 7 provide Remodulin infusion delivery rates for doses up to 155 ng/kg/min, based on patient weight, drug delivery rate and concentration. These tables may be used to select the most appropriate concentration and infusion rate for Remodulin.

Table 4

1.0 mg/ml Concentration of UT-15
MiniMed 407C pump Infusion Rate Setting (mls/hr) for 1.0 mg/ml UT-15

Patient Weight (kg)

Dose (ng/kg/min)	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
1.25	0.002	0.002	0.003	0.003	0.003	0.004	0.004	0.005	0.005	0.005	0.006	0.006	0.006	0.007	0.007	0.008
2.5	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
3.75	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021	0.023
5	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
6.25	0.009	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.024	0.026	0.028	0.030	0.032	0.034	0.036	0.038
7.5	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
8.75	0.013	0.016	0.018	0.021	0.024	0.026	0.029	0.032	0.034	0.037	0.039	0.042	0.045	0.047	0.050	0.053
10	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
11.25	0.017	0.020	0.024	0.027	0.030	0.034	0.037	0.041	0.044	0.047	0.051	0.054	0.057	0.061	0.064	0.068
12.5	0.019	0.023	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
13.75	0.021	0.025	0.029	0.033	0.037	0.041	0.045	0.050	0.054	0.058	0.062	0.066	0.070	0.074	0.078	0.083
15	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
16.25	0.024	0.029	0.034	0.039	0.044	0.049	0.054	0.059	0.063	0.068	0.073	0.078	0.083	0.088	0.093	0.098
17.5	0.026	0.032	0.037	0.042	0.047	0.053	0.058	0.063	0.068	0.074	0.079	0.084	0.089	0.095	0.100	0.105
18.75	0.028	0.034	0.039	0.045	0.051	0.056	0.062	0.068	0.073	0.079	0.084	0.090	0.096	0.101	0.107	0.113
20	0.030	0.036	0.042	0.048	0.054	0.060	0.066	0.072	0.078	0.084	0.090	0.096	0.102	0.108	0.114	0.120
21.25	0.032	0.038	0.045	0.051	0.057	0.064	0.070	0.077	0.083	0.089	0.096	0.102	0.108	0.115	0.121	0.128
22.5	0.034	0.041	0.047	0.054	0.061	0.068	0.074	0.081	0.088	0.095	0.101	0.108	0.115	0.122	0.128	0.135
23.75	0.036	0.043	0.050	0.057	0.064	0.071	0.078	0.086	0.093	0.100	0.107	0.114	0.121	0.128	0.135	0.143
25	0.038	0.045	0.053	0.060	0.068	0.075	0.083	0.090	0.098	0.105	0.113	0.120	0.128	0.135	0.143	0.150
27.5	0.041	0.050	0.058	0.066	0.074	0.083	0.091	0.099	0.107	0.116	0.124	0.132	0.140	0.149	0.157	0.165
30	0.045	0.054	0.063	0.072	0.081	0.090	0.099	0.108	0.117	0.126	0.135	0.144	0.153	0.162	0.171	0.180
32.5	0.049	0.059	0.068	0.078	0.088	0.098	0.107	0.117	0.127	0.137	0.146	0.156	0.166	0.176	0.185	0.195
35	0.053	0.063	0.074	0.084	0.095	0.105	0.116	0.126	0.137	0.147	0.158	0.168	0.179	0.189	0.200	0.210
37.5	0.056	0.068	0.079	0.090	0.101	0.113	0.124	0.135	0.146	0.158	0.169	0.180	0.191	0.203	0.214	0.225
40	0.060	0.072	0.084	0.096	0.108	0.120	0.132	0.144	0.156	0.168	0.180	0.192	0.204	0.216	0.228	0.240
42.5	0.064	0.077	0.089	0.102	0.115	0.128	0.140	0.153	0.166	0.179	0.191	0.204	0.217	0.230	0.242	0.255

NOTE: Blank spaces indicate that this concentration of UT-15 is inapproriate for the corresponding dose
The infusion rate for 1.0 mg/ml can be calculated using the following formula: Patient weight(kg) x dose(ng/kg/min) x 0.00006.
Shaded areas indicate the highest infusion rate supported by one syringe change every three days

Table 5 2.5 mg/ml Concentration of UT-15
MiniMed 407C pump Infusion Rate Setting (mls/hr) for 2.5 mg/ml UT-15

Patient Weight (kg)

Dose (ng/kg/min)	25	30	35	40	45	50	55	60	65	70	75	80	85	90	95	100
5	0.003	0.004	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
6.25	0.004	0.005	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
7.5	0.005	0.005	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
8.75	0.005	0.006	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
10	0.006	0.007	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
11.25	0.007	0.008	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
12.5	0.008	0.009	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
13.75	0.008	0.010	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
15	0.009	0.011	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
16.25	0.010	0.012	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
17.5	0.011	0.013	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
18.75	0.011	0.014	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
20	0.012	0.014	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
21.25	0.013	0.015	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
22.5	0.014	0.016	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
23.75	0.014	0.017	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
25	0.015	0.018	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
27.5	0.017	0.020	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
30	0.018	0.022	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
32.5	0.020	0.023	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
35	0.021	0.025	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
37.5	0.023	0.027	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
40	0.024	0.029	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096
42.5	0.026	0.031	0.036	0.041	0.046	0.051	0.056	0.061	0.066	0.071	0.077	0.082	0.087	0.092	0.097	0.102

NOTE: Blank spaces indicate that this concentration of UT-15 is inappropriate for the corresponding dose
The infusion rate for 2.5 mg/ml can be calculated using the following formula: Patient weight(kg) x dose(ng/kg/min) x 0.000024.

Table 6 5.0 mg/mL Concentration of UT-15
Pump Infusion Rate Setting (mL/hr) for 5.0 mg/mL UT-15

Patient Weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
10	0.004	0.005	0.005	0.006	0.007	0.007	0.008	0.008	0.009	0.010	0.010	0.011	0.011	0.012
12.5	0.005	0.006	0.007	0.008	0.008	0.009	0.010	0.011	0.011	0.012	0.013	0.014	0.014	0.015
15	0.006	0.007	0.008	0.009	0.010	0.011	0.012	0.013	0.014	0.014	0.015	0.016	0.017	0.018
17.5	0.007	0.008	0.009	0.011	0.012	0.013	0.014	0.015	0.016	0.017	0.018	0.019	0.020	0.021
20	0.008	0.010	0.011	0.012	0.013	0.014	0.016	0.017	0.018	0.019	0.020	0.022	0.023	0.024
22.5	0.009	0.011	0.012	0.014	0.015	0.016	0.018	0.019	0.020	0.022	0.023	0.024	0.026	0.027
25	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
27.5	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
30	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
32.5	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
35	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
37.5	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
40	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
42.5	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
45	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
47.5	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
50	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
55	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
60	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
65	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
70	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
75	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
80	0.034	0.038	0.043	0.048	0.053	0.058	0.062	0.067	0.072	0.077	0.082	0.086	0.091	0.096

The infusion rate for 5.0 mg/mL may be calculated using the following formula: Patient Weight(kg) x dose(ng.kg/min) x 0.000012.

Table 7 — 10.0 mg/mL Concentration of UT-15
Pump Infusion Rate Setting (mLs/hr) for 10.0 mg/mL UT-15

Patient Weight (kg)

Dose (ng/kg/min)	35	40	45	50	55	60	65	70	75	80	85	90	95	100
50	0.011	0.012	0.014	0.015	0.017	0.018	0.020	0.021	0.023	0.024	0.026	0.027	0.029	0.030
55	0.012	0.013	0.015	0.017	0.018	0.020	0.021	0.023	0.025	0.026	0.028	0.030	0.031	0.033
60	0.013	0.014	0.016	0.018	0.020	0.022	0.023	0.025	0.027	0.029	0.031	0.032	0.034	0.036
65	0.014	0.016	0.018	0.020	0.021	0.023	0.025	0.027	0.029	0.031	0.033	0.035	0.037	0.039
70	0.015	0.017	0.019	0.021	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.040	0.042
75	0.016	0.018	0.020	0.023	0.025	0.027	0.029	0.032	0.034	0.036	0.038	0.041	0.043	0.045
80	0.017	0.019	0.022	0.024	0.026	0.029	0.031	0.034	0.036	0.038	0.041	0.043	0.046	0.048
85	0.018	0.020	0.023	0.026	0.028	0.031	0.033	0.036	0.038	0.041	0.043	0.046	0.048	0.051
90	0.019	0.022	0.024	0.027	0.030	0.032	0.035	0.038	0.041	0.043	0.046	0.049	0.051	0.054
95	0.020	0.023	0.026	0.029	0.031	0.034	0.037	0.040	0.043	0.046	0.048	0.051	0.054	0.057
100	0.021	0.024	0.027	0.030	0.033	0.036	0.039	0.042	0.045	0.048	0.051	0.054	0.057	0.060
105	0.022	0.025	0.028	0.032	0.035	0.038	0.041	0.044	0.047	0.050	0.054	0.057	0.060	0.063
110	0.023	0.026	0.030	0.033	0.036	0.040	0.043	0.046	0.050	0.053	0.056	0.059	0.063	0.066
115	0.024	0.028	0.031	0.035	0.038	0.041	0.045	0.048	0.052	0.055	0.059	0.062	0.066	0.069
120	0.025	0.029	0.032	0.036	0.040	0.043	0.047	0.050	0.054	0.058	0.061	0.065	0.068	0.072
125	0.026	0.030	0.034	0.038	0.041	0.045	0.049	0.053	0.056	0.060	0.064	0.068	0.071	0.075
130	0.027	0.031	0.035	0.039	0.043	0.047	0.051	0.055	0.059	0.062	0.066	0.070	0.074	0.078
135	0.028	0.032	0.036	0.041	0.045	0.049	0.053	0.057	0.061	0.065	0.069	0.073	0.077	0.081
140	0.029	0.034	0.038	0.042	0.046	0.050	0.055	0.059	0.063	0.067	0.071	0.076	0.080	0.084
145	0.030	0.035	0.039	0.044	0.048	0.052	0.057	0.061	0.065	0.070	0.074	0.078	0.083	0.087
150	0.032	0.036	0.041	0.045	0.050	0.054	0.059	0.063	0.068	0.072	0.077	0.081	0.086	0.090
155	0.033	0.037	0.042	0.047	0.051	0.056	0.060	0.065	0.070	0.074	0.079	0.084	0.088	0.093

Note: Blank spaces indicate the this concentration of UT-15 is inappropriate for the corresponding dose. The infusion rate for the 10 mg/mL concentration can be calculated by using the following formula: Patient weight (kg) x dose (ng/kg/mL) x .000006.

(j) How Supplied

Remodulin™ is supplied in 20 mL multi-use vials at concentrations of 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL treprostinil, as sterile solutions in water for injection, individually packaged in a carton. Each mL contains treprostinil sodium equivalent to 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, or 10.0 mg/mL treprostinil. Unopened vials of Remodulin are stable until the date indicated when stored at 15 to 25°C (59 to 77°F).

During use, a single reservoir of Remodulin can be administered up to 72 hours at 37°C.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. If either particulate matter or discoloration is noted, Remodulin should not be administered.

20-mL vial containing treprostinil sodium equivalent to 1 mg treprostinil per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinil sodium equivalent to 2.5 mg treprostinil per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinil sodium equivalent to 5.0 mg treprostinil per mL, carton of 1 (NDC xxxx-xxxx-xx).

20-mL vial containing treprostinil sodium equivalent to 10.0 mg treprostinil per mL, carton of 1 (NDC xxxx-xxxx-xx).

US Patent No. 5,153,222 (Use Patent)

United Therapeutics Corp.
Research Triangle Park, NC 27709

REMODULIN manufactured by

Cook Pharmaceutical Solutions

Bloomington, IN 47403

For United Therapeutics Corp.

Research Triangle Park, NC 27709

Appendix B : Remodulin™ P01:04/05 Statistical Analysis Plan

United Therapeutics
CORPORATION

68 T.W. Alexander Drive. PO Box 14186
Research Triangle Park, NC 27709
tel 919.485.8350
fax 919.485.8352

GENERAL CORRESPONDENCE:
Statistical Analysis Plan for Protocols P01:04/P01:05

March 23, 2000

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research, HFD-110
Division of Cardio-Renal Drug Products
Attention: DOCUMENT CONTROL ROOM
1451 Rockville Pike
Rockville, Maryland 20857

Re: IND 36,704
UT-15 Injection
Serial No. 073

Dear Dr. Lipicky:

Reference is made to our November 15, 1999, Clinical/Nonclinical Pre-NDA Meeting and to our submission on January 17, 2000 (Serial No 065) of our draft statistical analysis plan for Dr. Hung's review. Reference is also made to the February 17, 2000, teleconference to review Dr. Hung's comments on the statistical analysis plan and our minutes of the teleconference provided to FDA February 24, 2000. Reference is lastly made to our submission of March 6, 2000 (Serial No. 072), of our final Statistical Analysis Plan (SAP) for Protocols P01:04 and P01:05.

Upon final review of the SAP prior to unblinding, we have the following adjustments to the SAP provided March 6, 2000:

- In addition to the descriptions of the handling of missing data in Table 8.3.1 on page 14 of the final analysis plan, if an exercise test is missing because "patient was too critically ill", the lowest standardized rank will be used for the nonparametric analysis and a distance of 0 meters will be used for the parametric analysis. Data missing for any other reason will have last standardized ranks carried forward for the nonparametric analyses and last observations carried forward for the parametric analyses. Values and ranks from the baseline assessment will be carried forward only for analyses on the "Pure Intent-to-Treat" population.

- The phrase "and use of steroid therapy to treat PHT at baseline" should be deleted on page 30 of the final analysis plan in Section 9.2.1 from step "1)" (this was an oversight, since it had already been deleted in Section 8.2).

- The phrase "rescue therapy with intravenous inotropes" will be changed to "rescue therapy with intravenous inotropes or prostaglandins" in Section 9.2.1, modification "3)" on page 32 of the final analysis plan. From review of the blinded data, we have identified five patients who received such rescue therapy during the study (14001, 16003, 20007, 50014, and 54017). Two additional secondary analyses will be performed using the same approach, but first disregarding use of diuretics as the basis for determining treatment failures, and then disregarding use of vasodilators, diuretics, digoxin, and oxygen as the basis for determining treatment failures.

In reference to "other protocol violations" which warrant the removal of a patient from the "Per-Protocol" population (see #5 on page 6 of the final analysis plan), we have identified the following patients:

Patient	Reason
10021	Patient misdiagnosed as PPH, but subsequently had clear interstitial lung disease.
16003	Patient received rescue therapy with dobutamine during the last few days of the study.
50014	Patient received rescue therapy with dobutamine during the last few days of the study.

We will be unblinding and running preliminary analyses prior to cleaning up all the pertinent efficacy data. However, we have identified the following specific outstanding items to be cleaned up:

Patient	Issue
08006	After further review of the adverse event data, reason for discontinuation (p. 55 of the CRF) should be changed from "adverse experience" to "clinical deterioration"
09006	"
10017	"
15003	"
53022	"
54005	"
54028	"
58001	"
58006	"
64003	"
65006	"
54020	Reason for missing Week 1 Exercise Test will be clarified
15006	Reason for missing Week 12 Exercise Test will be clarified
19001	Reason for missing Week 6 Exercise Test will be clarified
20007	Reason for missing Week 1 Exercise Test will be clarified
03503	Reason for missing Week 1 Exercise Test will be clarified
60014	Reason for missing Week 1 Exercise Test will be clarified

Should you have any questions concerning the enclosed information, please contact me at 919-485-8350, ext. 192.

Sincerely,

Dean Bunce
Associate Director of Regulatory Affairs

Via Facsimile (301 594-5495) and Federal Express (Tracking # 8196 4929 4430)

AN INTERNATIONAL, MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL PLACEBO-CONTROLLED COMPARISON OF THE SAFETY AND EFFICACY OF CHRONIC SUBCUTANEOUS UT-15 PLUS CONVENTIONAL THERAPY TO CONVENTIONAL THERAPY IN PATIENTS WITH PULMONARY HYPERTENSION

A 12-WEEK STUDY

Analysis Plan for P01:04 and P01:05

UNITED THERAPEUTICS CORPORATION

Original Protocol Date:	14 April 1998
Revised Version Date:	07 May 1998
Amendment No. 1 Date:	15 September 1998
Amendment No. 2 Date:	09 November 1998
Amendment No. 3 Date:	22 December 1998
Original Analysis Plan Date:	9 November 1999
Prepared By:	Michael D. Thorn, DrPH, Statistical Resources, Inc.
Revised Analysis Plan Date:	6 March 2000
Revised By:	Carl Arneson, United Therapeutics Corp.

TECHNICAL APPROVERS:

David Mottola, Director of Clinical and Scientific Affairs	3-6-00 Date of Approval
Carl Arneson, Manager of Biostatistics and Data Management	06 MAR 2000 Date of Approval

TABLE OF CONTENTS

ABBREVIATIONS AND UNITS

AE	Adverse Event
ALT (SGPT)	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST (SGOT)	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CI	Cardiac Index
cm	Centimeters
CO	Cardiac Output
CO_2	Carbon Dioxide
CRF	Case Report Form
CRO	Contract Research Organization
dL	Deciliter
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
°F	Degrees Fahrenheit
FDA	Food and Drug Administration (U.S.)
Hb	Hemoglobin
Hg	Mercury
H_o	Null Hypothesis
HR	Heart Rate
INR	International Normalization Ratio
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
IU	International Units
kg	Kilogram
L	Liters
LDH	Lactate Dehydrogenase
LOCF	Last Observation Carried Forward
m	Meters
mg	Milligrams
mITT	Modified Intent-to-Treat
mL	Milliliters
MAP	Mean Arterial Blood Pressure

ABBREVIATIONS AND UNITS

min	Minute
mm	Millimeters
mmol	Millimole
NDA	New Drug Application
ng	Nanogram
NYHA	New York Heart Association
PAPd	Diastolic Pulmonary Arterial Pressure
PAPm	Mean Pulmonary Arterial Pressure
PAPs	Systolic Pulmonary Arterial Pressure
PAS	Pulmonary Arterial Saturation
PBF	Pulmonary Blood Flow
PBFI	Pulmonary Blood Flow Index
PCWPm	Mean Pulmonary Capillary Wedge Pressure
PHT	Pulmonary (Arterial) Hypertension
pITT	Pure Intent-to-Treat
PPH	Primary Pulmonary Hypertension
PVR	Pulmonary Vascular Resistance
PVRI	Pulmonary Vascular Resistance Index
PVS	Pulmonary Venous Saturation
QoL	Quality of Life
RAPm	Right Atrial Pressure
RBC	Red Blood Cell
SAPd	Diastolic Systemic Arterial Pressure
SAPm	Mean Systemic Arterial Pressure
SAPs	Systolic Systemic Arterial Pressure
SBF	Systemic Blood Flow
SBFI	Systemic Blood Flow Index
sec	Seconds
SI	Stroke Index
SV	Stroke Volume
SVR	Systemic Vascular Resistance
SVRI	Systemic Vascular Resistance Index
Temp	Temperature
TPR	Total Pulmonary Resistance
TPRI	Total Pulmonary Resistance Index
WHO	World Health Organization

1 PREFACE

This document describes the planned analyses for P01:04 and P01:05, which are two concurrent, essentially identical pivotal studies. All of the analyses described in this document will be performed separately for each study for the individual study reports. In addition, all analyses involving the primary efficacy endpoint, and possibly other select analyses, will be performed on the data from both studies combined (as described in section 8.1) for the purpose of assessing overall results. However, this document does not describe all intended analyses for the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) sections of the NDA.

2 STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this 12-week study is to determine the effects of continuous subcutaneous infusions of UT-15 on exercise capacity in severely ill patients with pulmonary arterial hypertension (renamed from "pulmonary vascular disease" based on a WHO reclassification of the disease). The primary endpoint of this study is the total distance walked during a six-minute walk exercise test at Week 12 of the study.

A principal reinforcing objective is to determine the effects of UT-15 on signs and symptoms of pulmonary arterial hypertension. Signs and symptoms of pulmonary arterial hypertension will be evaluated in two ways: (1) changes in frequency and/or severity of symptoms and (2) time to discontinuation of study drug due to patient's clinical deterioration, due to transplantation secondary to deterioration or due to death. Principal reinforcing endpoints include change from baseline in individual signs and symptoms of PHT, change from baseline in Dyspnea-Fatigue Index, and time from randomization to discontinuation of study drug due to clinical deterioration, transplantation, or death.

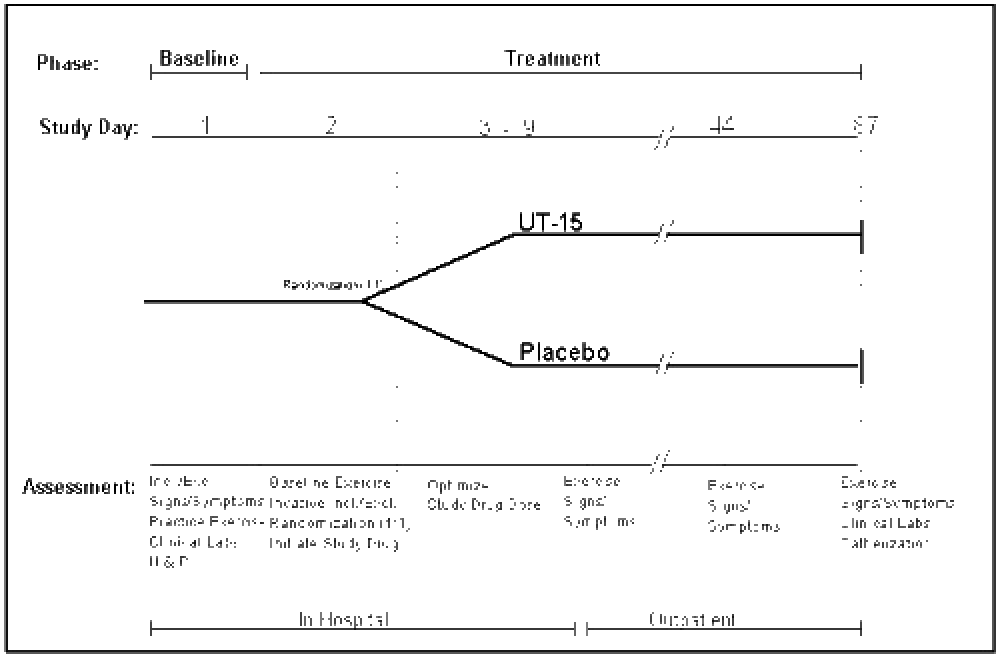
The secondary objective is to assess the effects of continuous subcutaneous infusions of UT-15 on hemodynamics and Quality of Life.

The tertiary objective of this study is to assess the effects of patient factors (e.g. gender, age, race) on the disposition of UT-15 and to evaluate pharmacokinetic drug-drug interactions. Analysis of population pharmacokinetics will be employed.

3 STUDY DESIGN

The P01:04 and P01:05 trials have identical international, multicenter, double blind, randomized, parallel, placebo-controlled designs for comparing UT-15 plus conventional therapy to conventional therapy alone. Two hundred and twenty-four patients with pulmonary arterial hypertension who are not receiving Flolan or other intravenous, inhaled or oral prostaglandins or prostaglandin analogues will be enrolled and randomized for entry in each study. Each study is divided into the Screening, Baseline and Treatment Phases, as shown in Figure 3.1.

Figure 3.1



After optimization of conventional oral PHT therapy, patients meeting all inclusion/exclusion criteria during the Screening Phase will enter the Baseline Phase during which baseline exercise capacity, Quality of Life, hemodynamic parameters, and clinical signs and symptoms of the disease

will be assessed. Immediately after providing baseline hemodynamic measurements and meeting all hemodynamic inclusion/exclusion criteria, patients will be randomized (1:1) to receive either (1) conventional PHT therapy plus a continuous subcutaneous infusion of UT-15 or (2) conventional PHT therapy plus a continuous subcutaneous infusion of placebo. Randomization will be stratified for baseline exercise and etiology of pulmonary arterial hypertension. In patients with secondary forms of pulmonary hypertension, randomization will also be stratified for use of vasodilators at baseline. During the 12-Week Treatment Phase, exercise capacity, Quality of Life and clinical symptoms of pulmonary arterial hypertension will be assessed at specified times and blood will be drawn for pharmacokinetic analysis. Safety will be monitored throughout the 12 weeks.

After completing all Week 12 assessments of the Treatment Phase, each patient will be dismissed from study and subsequently become eligible for the P01:06 open-label study. To aid in the transition of patients from P01:04/P01:05 to P01:06, the treatment assignment for each patient will be unmasked to the treating physician. To minimize the possibility of bias, two procedures will be strictly followed at each center: (1) treatment assignment will remain masked to the individual administering the exercise tests until all patients have completed the study and (2) exercise data will be secured by the individual administering the exercise tests and not revealed to other study personnel, including the principal investigator, until all patients have completed the study. Each patient who completes either study (i.e., who completes all Week 12 Treatment Phase assessments), regardless of treatment assignment, will have the option of receiving UT-15 in the open continuation study (P01:06). Patients who are dismissed prior to completing all week 12 assessments are not eligible to receive UT-15 in an open continuation study.

4 SEQUENCE OF PLANNED ANALYSES

Completed and monitored CRFs are forwarded to an independent data management CRO for processing. The final quality-assured database used in the analyses described in this document will be available to the sponsor approximately one month after the last patient completes the Week 12

assessment of the P01:05 study. Prior to this time, preliminary data (without actual treatment assignment information) will be available to an independent statistical CRO to allow for the set-up of the analysis programming. However, the actual treatment assignments will not be available to the statistical CRO or sponsor until the final data are locked and issued by the CRO handling data management.

Adverse event, death, and demographic data were provided to an independent statistical contractor to provide analyses to an independent data safety monitoring board (DSMB) on three occasions during the studies (see Section 7). A random identifier of treatment group (i.e., "A" or "B") was provided with these data, and analyses were performed using this identifier, but the actual corresponding treatment information (i.e., "UT-15" or "Placebo") was not disclosed. Neither these data, nor the analyses, were made available to anyone other than the contractor performing the analyses and DSMB.

5 SAMPLE SIZE CONSIDERATIONS

The effect of UT-15 on exercise capacity at Week 12, as measured by distance walked in six minutes, is the primary endpoint for this trial and is the basis on which the sample size has been estimated.

The results of exercise tests, as measured by the Six-Minute Walk test, in 81 NYHA Class III/IV patients, who received chronic Flolan for 12 weeks, were used as the basis of sample size estimates. Distance walked by 41 patients with PPH who received Flolan improved by 30 meters over baseline compared to a 15-meter decrease in exercise in 40 patients who did not receive Flolan; standard deviation in this trial was approximately 75 meters. Assuming a slightly larger between-treatment difference of 55 meters in patients who receive UT-15 compared to placebo, a larger standard deviation of 110 meters, a type I (alpha) error of 0.05 (i.e., two-sided p-value of less than 0.05), a 95% power to detect this difference, and a non-parametric (Mann-Whitney; uniform distributions) adjustment to a two sample Student's t-test, 105 patients per treatment group were required for this trial.

Sample size calculations were performed using PASS™ version 6.0 (NCSS, 329 North 1000 East, Kaysville, Utah).

6 ANALYSIS POPULATIONS

The "Pure Intent-to-Treat" (or "*p*ITT") population is defined as all subjects randomized into either study, and all patients will be counted as being in the group to which they were randomized, regardless of the treatment they were actually given, or whether any study drug was given at all. All original stratification information used in the randomization procedure will be used, regardless of whether it was later found to be incorrect.

The "Modified Intent-to-Treat" (or "*m*ITT") population is the same as the "*p*ITT" population, except that patients who never received either study medication will be excluded and incorrect stratification information will be corrected for the analysis. In addition, efficacy data for any patient who was inadvertently given the alternative treatment during the trial (i.e., crossed-over) due to errors in resupply of study medication will be censored at the time of cross-over (by not having data after cross-over included in the analyses).

The "Per-Protocol" population is defined as all patients in either study actually receiving study drug for at least 8 weeks and who had Baseline and Week 12 exercise test assessments or normally discontinued due to death, transplantation or clinical deterioration, excluding patients with major protocol violations, and excluding patients who were not receiving study drug during their Week 12 exercise test due to premature discontinuation. Patients will be counted as being in the group corresponding to the treatment they actually received at the start of the dosing period. Patients who crossed-over to the alternative treatment during the trial will be excluded. Patients with the following protocol violations will be excluded:

1) Violation of inclusion criteria 3 and 6 (values on p. 14 of the CRF will be used to verify; PCWPm will not be used as the basis for violation)

2) Violations of exclusion criteria 7, 9, 10, 11, and12

3) Use of any prostaglandins or their analogues for the treatment of pulmonary hypertension (as collected on the "Concomitant PHT Medications" pages [pp. 50.*] of the CRF) within seven days prior to the Week 12 exercise test.

4) Chronic concomitant use (use during at least 5 consecutive days of the dosing period) of intravenous or inhaled medications to treat pulmonary hypertension (as collected on the "Concomitant PHT Medications" pages [pp. 50.*] of the CRF)

5) Other protocol violations may be considered on an individual patient basis prior to unblinding

The definition of the "Per-Protocol" population may be modified slightly prior to unblinding if less than 75% of all patients randomized into either trial fit the current definition.

The "Safety" population is defined as all patients in either study actually receiving study drug, and all patients will be counted as being in the group corresponding to the treatment that they actually received. If a patient received UT-15 at any point during the study, they will be counted in that treatment group.

The "PK" population will include all patients with non-missing UT-15 concentration data.

Several randomization issues were identified during these trials. The statistical management of each specific issue for each of the analysis populations is presented in Table 6.1.

Table 6.1
Statistical Management of Randomization Issues by Analysis Population

Issue	mITT	pITT	Per-Protocol	Safety
Randomized manually to correct treatment	Included	Included	Included	Included
Randomized manually, received incorrect treatment weeks 7-12	Included; efficacy censored at Week 6	Included	Excluded	Included
Incorrect stratification information	Included; stratification information corrected	Included; stratification information not corrected	Included; stratification information corrected	Included; stratification information corrected
Only one assignment available at site	Included	Included	Included	Included

All of the above populations will be prefixed by "P01:04", "P01:05", or "Pooled", depending on whether patients come from the P01:04, P01:05, or combined studies.

Any of the above populations may be suffixed by "PPH", denoting a subset of any of the populations with a diagnosis of PPH at baseline (as entered on page 4 of the CRF).

All study population analyses, efficacy analyses, and quality of life analyses (described in Sections 9.1, 9.2, and 9.3, respectively) will be performed on both the "P01:04 *m*ITT" and "P01:05 *m*ITT" populations. In addition, all analyses involving the primary efficacy endpoint (described in Section 9.2.1), and possibly other select analyses, will be performed on the "Pooled *m*ITT" and "Pooled *m*ITT PPH" populations (see Section 8.1 for a discussion of the use of the "Pooled" populations versus the individual study populations in the efficacy analyses). To examine the robustness of the primary results, all primary analyses will additionally be performed on all "*p*ITT" and "Per-Protocol" populations. All safety analyses (described in Section 9.4) will be performed on both the "P01:04 Safety" and "P01:05 Safety" populations. Safety analyses on pooled data will be handled separately in the ISS section of the NDA. All pharmacokinetic analyses will be performed on the "Pooled PK" population.

7 INTERIM ANALYSES

No interim analyses of efficacy were planned or performed.

Interim safety analyses were planned and performed after 20%, 40%, and 60% of the planned number of patients in the combined studies had completed the Week 12 assessment. All such analyses were performed on combined study ("Pooled") data. In addition, for the first two interim looks, analyses were also performed on the individual study data. For all analyses, the treatment groups were identified only as "Group A" and "Group B". The true identities of the treatments corresponding to these groups were not disclosed. All analyses were performed by an independent statistical contractor. Results were submitted to and reviewed only by members of an independent DSMB, which consisted of one statistician and two independent clinicians who were not otherwise involved in either study. These analyses consisted only of adverse event, death, and demographic data.

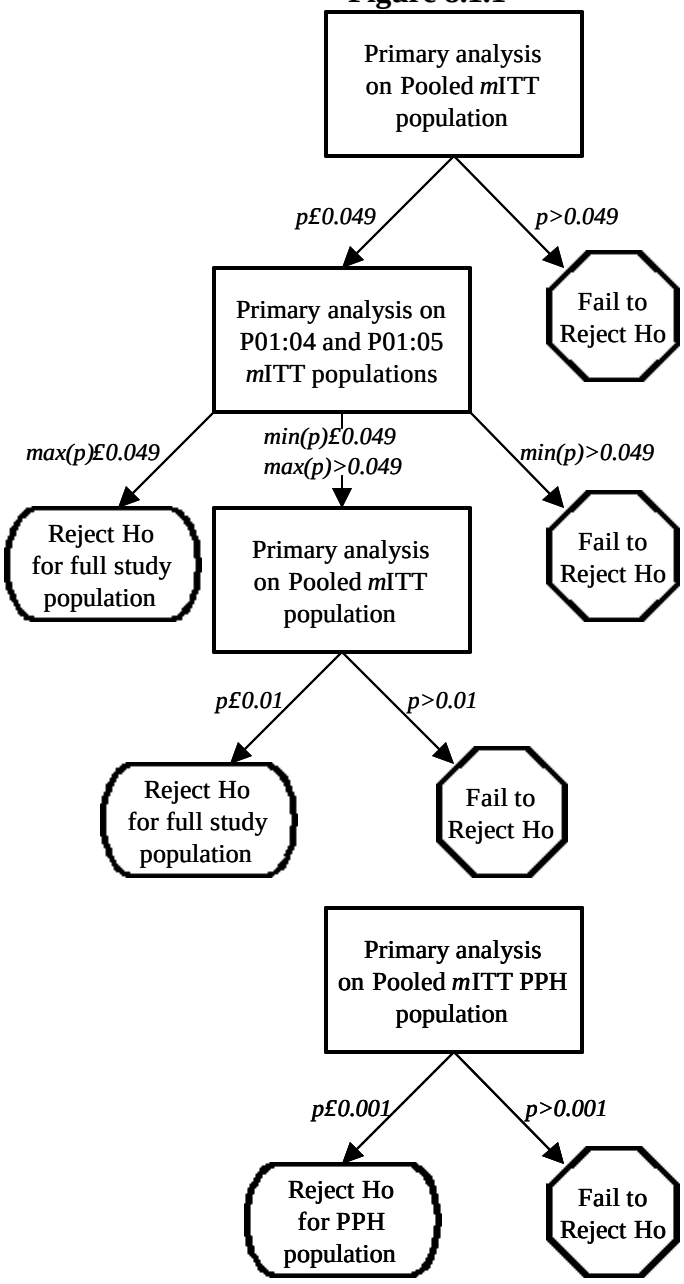
8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

8.1 Pooled versus Individual Study Analyses

The primary analysis (described in Section 9.2.1) will first be performed on the "Pooled *m*ITT" population. If this analysis is significant in favor of UT-15 at the 0.049 (two-sided) level, then the analysis will be repeated on both the "P01:04 *m*ITT" population and the "P01:05 *m*ITT" population. If each additional analysis is significant in favor of UT-15 at the 0.049 (two-sided) level, then the overall null hypothesis of no treatment difference will be rejected for the entire study population. However, if one analysis is significant in favor of UT-15 at the 0.049 (two-sided) level and the other is not, then the "Pooled *m*ITT" analysis will be re-assessed at the 0.01 (two-sided) level. If the "Pooled *m*ITT" analysis is significant in favor of UT-15 at the 0.01 (two-sided) level, then the overall null hypothesis of no treatment difference will be rejected for the entire study population. If not, then the same analysis will be done on the "Pooled *m*ITT PPH" population. If this analysis is significant at the 0.001 (two-sided) level, then the overall null

hypothesis of no treatment difference will be rejected for the subset of the study population with a diagnosis of PPH at baseline. This approach is illustrated in Figure 8.1.1:

Figure 8.1.1



Ho: No difference between UT-15 and placebo with respect to the primary endpoint

If the null hypothesis is rejected based on having p-values below 0.049 for both individual studies in the above approach, then both studies will be considered separately for the purposes of evaluating detailed results. Otherwise, additional analyses of principal reinforcing endpoints, secondary efficacy, and quality of life (described in Sections 9.2.2, 9.2.3, and 9.3) will be done on the pooled data in addition to the individual study data, but the results from the analyses on pooled data will be emphasized in the report. Analyses will be done on data from the various populations as shown in Table 8.1.1.

Table 8.1.1
Planned Analyses by Analysis Population

	P01:04	**P01:05**	**Pooled**
***m*ITT**	**9.1** Study Population **9.2** Efficacy **9.3** Quality of Life	**9.1** Study Population **9.2** Efficacy **9.3** Quality of Life	**9.2.1** Primary Efficacy **9.2.2** Principal Reinforcing Efficacy* **9.2.3** Secondary Efficacy* **9.3** Quality of Life*
***p*ITT**	**9.2.1** Primary Efficacy***	**9.2.1** Primary Efficacy***	**9.2.1** Primary Efficacy***
Per-Protocol	**9.2.1** Primary Efficacy***	**9.2.1** Primary Efficacy***	**9.2.1** Primary Efficacy***
Safety	**9.4** Safety	**9.4** Safety	
***m*ITT PPH**			**9.2.1** Primary Efficacy **9.2.2** Principal Reinforcing Efficacy** **9.2.3** Secondary Efficacy** **9.3** Quality of Life**
***p*ITT PPH**			**9.2.1** Primary Efficacy***
Per-Protocol PPH			**9.2.1** Primary Efficacy***
PK			**9.5** Pharmacokinetics

* if p>0.049 for either P01:04 or P01:05, but p≤0.01 for pooled data (with respect to the primary analysis)
** if p>0.049 for either P01:04 or P01:05, p>0.01 for pooled data, but p≤0.001 for pooled PPH data (with respect to the primary analysis)
*** primary and secondary analyses only; no descriptive summaries

8.2 Covariates

The primary (nonparametric) and secondary (parametric) comparisons of six-minute walk distances at Week 12 (see Section 9.2.1) will be adjusted for six-minute walk distance during the baseline assessment (continuous), center (categorical), etiology of pulmonary hypertension (dichotomous – PPH vs. other), and vasodilator use at baseline (dichotomous – yes vs. no). Etiology of pulmonary hypertension will not be used when this analysis is applied to subsets of PPH patients. Center will be broken into categories corresponding to unique investigator site numbers. Centers that were used in both P01:04 and P01:05 will be treated as separate categories for the pooled analyses. Centers with less than approximately six patients in the "Per-Protocol" population will be pooled (roughly by geographical region) as follows:

Pooled Center ID:	**Centers:**
401	01 – Dr. Sean Gaine (Baltimore, MD)06 – Dr. David Badesch (Denver, CO)13 – Dr. Joel Wirth (Portland, ME) 21 – Dr. Nicholas Hill (Providence, RI) 23 – Dr. Dunbar Ivy (Denver, CO)
402	11 – Dr. Romona Doyle (Stanford, CA) 12 – Dr. Teresa DeMarco (San Francisco, CA) 15 – Dr. Greg Elliott (Salt Lake City, UT)
403	17 – Dr. David Langleben (Montreal, Quebec) 18 – Dr. David Ostrow (Vancouver, BC)
404	19 – Dr. Robert Schilz (Cleveland, OH) 22 – Dr. Ben deBoisblanc (New Orleans, LA)
501	51 – Prof. Meinhard Kneussl (Wien, Austria) 52 – Dr. Marion Delcroix (Leuven, Belgium) 55 – Dr. Marius Hoeper (Hannover, Germany)
502	56 – Dr. Neville Berkman (Jerusalem, Israel) 57 – Dr. Issahar Ben-Dov (Tel Hashomer, Israel) 58 – Dr. Mordechai Kramer (Petach Tikvah, Israel)
503	64 – Dr. Tim Higenbottam (Sheffield, UK) 66 – Dr. Paul Corris (Newcastle Upon Tyne, UK)
504	77 – Dr. Ivan Robbins (Nashville, TN) 78 – Dr. Victor Tapson (Durham, NC) 80 – Dr. Robert Bourge (Birmingham, AL)

Pooled Center ID:	Centers:
505	79 – Dr. Adaani Frost (Houston, TX) 89 – Dr. Robert Schilz (Cleveland, OH) 90 – Dr. Julio Sandoval (Mexico) 92 – Dr. Ben deBoisblanc (New Orleans, LA)
506	72 – Dr. Robyn Barst (New York, NY) 73 – Dr. Stuart Rich (Chicago, IL) 75 – Dr. Michael McGoon (Rochester, MN) 86 – Dr. Srinivas Murali (Pittsburgh, PA) 87 – Dr. David Langleben (Montreal, Quebec) 91 – Dr. Nicholas Hill (Providence, RI)
507	74 – Dr. Ronald Oudiz (Torrance, CA) 81 – Dr. Romona Doyle (Stanford, CA) 82 – Dr. Teresa DeMarco (San Francisco, CA) 84 – Dr. Richard Channick (San Diego, CA) 85 – Dr. Greg Elliott (Salt Lake City, UT) 94 – Dr. Shelley Shapiro (Los Angeles, CA)

Etiology of pulmonary hypertension will be determined from the "PHT History" page (p. 4) of the CRF (based on whether "PPH" was specified as the current diagnosis). Vasodilator use at baseline will be determined from the "Concomitant PHT Medications" pages (pp. 50.*) of the CRF (see Section 8.4 for definition of relevant vasodilators), with a start date on or before the date of initiation of study drug or an indication that it was "Ongoing at Start of Study".

Further exploratory analyses may be performed using sex, race, age, baseline hemodynamics, NYHA class, specific etiology, groupings of geographic regions (e.g., "North America" vs. "Rest of World" and "Europe" vs. "Rest of World"), and chronic concomitant use (use of drug at least 75% of the time during the dosing period) of vasodilators, anticoagulants, diuretics, and digoxin to treat pulmonary hypertension (as collected on the "Concomitant PHT Medications" pages [pp. 50.*] of the CRF), and chronic concomitant use of analgesics (as collected on any of the concomitant medication pages [pp. 50.*, 51.*, 52.*]; see Section 8.4 for definitions of these classes)) as covariates in comparisons of 6-minute walk data at Week 12.

Unless otherwise specified, other analyses on principal reinforcing or secondary endpoints will not be adjusted for covariates.

8.3 Premature Discontinuation and Missing Data

Patients may not complete the full 12 weeks of treatment with UT-15 or Placebo for the following reasons: death, clinical deterioration sufficient to be prematurely discontinued from study, transplant, accident unrelated to disease, adverse event, lost to follow-up and/or withdrawal of consent. Patients who die, receive a transplant or who must be rescued from study due to clinical deterioration will be analyzed as treatment failures and no further data will be collected. For the purposes of the primary (nonparametric) analysis on six-minute walk distance at Week 12, lowest standardized rank (see procedure described in Section 9.2.1) will be used. For the secondary (parametric) analysis on six-minute walk distance at Week 12, 0 meters will be used.

Patients who had an accident that limits exercise (e.g. traffic accident) are not considered treatment failures, however their ability to provide data on assigned treatment ended at the time of accident; only general well-being of these patients at Week 12 will be recorded. The standardized rank from the last exercise assessment will be carried forward to Week 12 for the primary (nonparametric) analyses. The last observation will be carried forward for the secondary (parametric) analyses. Patients who are dismissed from study because of an adverse event will be followed for 12 weeks and exercise evaluated. For the primary (nonparametric) analyses, the standardized rank from the last exercise test performed prior to being dismissed from study will be carried forward. For the secondary (parametric) analyses, the last observation prior to being dismissed from the study will be carried forward. It is unlikely that a patient will be lost to follow-up or will withdraw consent. However, under these circumstances, every effort will be made to assess exercise at 12 weeks and/or assess the patient's well being. If Week 12 data are not available, the standardized rank from the last exercise test performed will be carried forward for the primary (nonparametric) analyses, and the last observation will be carried forward for the secondary (parametric) analyses.

Patients were required to have a baseline Six Minute Walk assessment in order to be randomized into the studies, so missing baseline values are not expected. Except in cases where a patient has died, received a transplant, or

were rescued from the study due to clinical deterioration, patients who are missing all post-baseline Six Minute Walk assessments will be excluded from the primary and secondary analyses of the primary endpoint for the "*m*ITT" and "Per-Protocol" populations, and the baseline assessment will be used as the basis for any "last standardized rank carried forward" or "last observation carried forward" imputation for the "*p*ITT" population.

Methods that will be used in each case to address missing exercise data for the primary and secondary protocol specified analyses on six-minute walk distance at Week 12 are summarized in Table 8.3.1.

Table 8.3.1

Handling of Missing Week 12 Six-Minute Walk Data

Event	**Value Used for Primary (Nonparametric) Analysis**	**Value Used for Secondary (Parametric) Analysis**
Death within 12 weeks; excluding transplantation and accidents	Lowest Standardized Rank	0 Meters
Clinical deterioration within 12 weeks; excluding transplantation and accidents	Lowest Standardized Rank	0 Meters
Transplantation	Lowest Standardized Rank	0 Meters
Accident*	Last Standardized Rank Carried Forward	LOCF
Adverse Event (Survivors at Week 12)*	Last Standardized Rank Carried Forward**	LOCF**
Lost to Follow-up (Survivors at Week 12)*	Last Standardized Rank Carried Forward***	LOCF***
Consent withdrawn (Survivors at Week 12)*	Last Standardized Rank Carried Forward***	LOCF***

Note: Standardized rank = [Rank]/[#Ranked +1] (so it is between 0 and 1)

* Patients who are missing all post-Baseline assessments will be excluded for the "*m*ITT" and "Per-Protocol" populations.

** Last rank/observation prior to dismissal from study will be used, even if the Week 12 assessment was done.

*** Last non-missing rank/observation will be carried forward only if the Week 12 assessment is not available.

Additional analyses on the primary endpoint will be performed where the last observation and last standardized rank assigned will be carried forward to Week 12 for all patients who discontinue prematurely for any reason.

No further attempts will be made to account for missing data in any secondary analyses.

8.4 Derived and Transformed Data

The following derivations and/or transformations will be used in the analyses:

Baseline Vital Signs:

	Formula	Units
BSA	$= 0.007184 \times [Wt(kg)]^{0.425} \times [Ht(cm)]^{0.725}$	m^2

Hemodynamic Parameters:

	Formula	Units
Temp	$= (°F - 32)/1.8$	°C
CO	$= \left\{\begin{array}{l}\text{CO Fick [if present]}\\ \text{Missing [otherwise]}\end{array}\right\}$ [for shunt patients] $= \left\{\begin{array}{l}\text{CO Thermodilution [if present]}\\ \text{CO Fick [otherwise]}\end{array}\right\}$ [otherwise]	L/min
CI	$= \frac{CO}{BSA}$	L/min/m^2
SBF	$= \frac{O_2\ Consumption}{0.136 \times (SaO_2 - SvO_2) \times Hb[\ g/\ dL]}$	L/min
SBFI	$= \frac{SBF}{BSA}$	L/min/m^2
PBF	$= \frac{O_2\ Consumption}{0.136 \times (PVS - PAS) \times Hb[\ g/\ dL]}$	L/min
PBFI	$= \frac{PBF}{BSA}$	L/min/m^2
SVR	$= \frac{(SAPm - RAPm)}{SBF}$ [for shunt patients] $= \frac{(SAPm - RAPm)}{CO}$ [otherwise]	mm Hg/(L/min)
SVRI	$= \frac{(SAPm - RAPm)}{SBFI}$ [for shunt patients] $= \frac{(SAPm - RAPm)}{CI}$ [otherwise]	mm Hg/(L/min/m^2)

TPR	$= \frac{PAPm}{PBF}$ [for shunt patients] $= \frac{PAPm}{CO}$ [otherwise]	mm Hg/(L/min)
TPRI	$= \frac{PAPm}{PBFI}$ [for shunt patients] $= \frac{PAPm}{CI}$ [otherwise]	mm Hg/(L/min/m^2)
PVR	$= \frac{(PAPm - PCWPm)}{PBF}$ [for shunt patients] $= \frac{(PAPm - PCWPm)}{CO}$ [otherwise]	mm Hg/(L/min)
PVRI	$= \frac{(PAPm - PCWPm)}{PBFI}$ [for shunt patients] $= \frac{(PAPm - PCWPm)}{CI}$ [otherwise]	mm Hg/(L/min/m^2)
SV	$= \frac{CO}{HR} \times 1000$	mL/beat
SI	$= \frac{CI}{HR} \times 1000$	mL/beat/m^2

Concomitant Medications:

Drug Class	**Definition**
Vasodilators	ATC Level 2 Classifications: PERIPHERAL VASODILATORS CALCIUM CHANNEL BLOCKERS AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM **-or-** ATC Level 3 Classifications: VASODILATORS USED IN CARDIAC DISEASES **-or-** ATC Level 4 Classifications: ALPHA – ADRENOCEPTOR BLOCKING AGENTS SELECTIVE BETA-2-ADRENOCEPTOR AGONISTS **-or-** Generic Drug Terms: ADENOSINE
Calcium Channel Blockers	ATC Level 2 Classifications: CALCIUM CHANNEL BLOCKERS
Other Vasodilators	Vasodilators **not** classified as ATC Level 2: CALCIUM CHANNEL BLOCKERS
Steroids	• ATC Level 2 Classifications: CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS CORTICOSTEROIDS FOR SYSTEMIC USE **-or-** ATC Level 4 Classification of CORTICOSTEROIDS • Route of Administration **not** topical ("TOP")

Drug Class	Definition
Diuretics	ATC Level 2 Classifications: DIURETICS
Anticoagulants	ATC Level 2 Classifications: ANTITHROMBOTIC AGENTS
Digoxin	ATC Level 4 Classifications: DIGITALIS GLYCOSIDES
Oxygen	Generic Drug Terms: OXYGEN
Analgesics	ATC Level 2 Classifications: ANALGESICS

8.5 Assessment Windows

For any data summarized by scheduled visit, visit identifiers will be taken directly from the CRF, provided that the actual assessment date falls within a predefined assessment window. In the event that the visit identifier from the CRF is not available or cannot be used, scheduled visits will be defined by these predefined assessment windows. If more than one observation per patient falls within the same assessment window, then the observation closest to the target study day will be used. If two observations are equally close to the target study day, the latest observation will be used. The scheduled visits, as recorded on the CRFs, and the corresponding target days and study day intervals are specified in the following tables:

Table 8.5.1

Assessment Windows for Scheduled Visits

Visit	Target Study Day	Study Day Interval
Labs, ECGs, and Hemodynamics:		
Screening/Baseline	2	Study Day ≤ 2
Week 12	86	72 ≤ Study Day ≤ 100
Quality of Life:		
Screening/Baseline	2	Study Day ≤ 2
Week 6	44	30 ≤ Study Day ≤ 58
Week 12	86	72 ≤ Study Day ≤ 100
PHT Signs and Symptoms, Dyspnea-Fatigue, Six-Minute Walk, and Borg Dyspnea Score:		
Screening/Baseline	2	Study Day ≤ 2
Week 1	9	3 ≤ Study Day ≤ 16
Week 6	44	30 ≤ Study Day ≤ 58
Week 12	86	72 ≤ Study Day ≤ 100
Chronic Infusion Site Symptoms:		
Week 1	9	3 ≤ Study Day ≤ 12
Week 2	16	13 ≤ Study Day ≤ 19
Week *n* (for *n*=3,…,11)	(7x*n*)+2	(7x*n*)-1 ≤ Study Day ≤ (7x*n*)+5
Week 12	86	83 ≤ Study Day ≤ 100

Note: Study Day = (Assessment Date) - (Randomization Date) + 2

Vital signs were scheduled to be taken immediately prior to the start of study drug infusion, and then at 15 min, 30 min, 1 hour, 2 hours, 4 hours, and 8 hours after initiation of study drug. Further assessments were to be taken at 2 hours and 4 hours after the next two dose increases during the dose-optimization phase. Assessment windows for these data will be defined as follows:

Table 8.5.2

Assessment Windows for Dose Optimization Vital Sign Measurements

Assessment	**Target Time* (minutes)**	**Time* Interval (minutes)**
Initial Dose:		
Prior to Study Drug	0	-60 ≤ Time ≤ 0
15 min	15	0 < Time ≤ 20
30 min	30	20 < Time ≤ 45
1 hour	60	45 < Time ≤ 90
2 hours	120	90 < Time ≤ 180
4 hours	240	180 < Time ≤ 360
8 hours	480	360 < Time ≤ 600
First Dose Increase:		
2 hours	120	60 < Time ≤ 180
4 hours	240	180 < Time ≤ 360
Second Dose Increase:		
2 hours	120	60 < Time ≤ 180
4 hours	240	180 < Time ≤ 360

* Time = (Assessment Date & Time) - (Date & Time of Current Dose) in minutes

9 DETAILS OF ANALYSES

All the data collected in the CRF will be listed. Unless otherwise specified in Section 9, listings will be sorted by investigator site number, treatment group, patient number, and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), and study day. For data collected on a fixed schedule, the assessment identifier (see Section 8.4) will also be included on the listing. Redundant observations within an assessment window and observations that do not fall within any predefined assessment window (and will, therefore, be excluded from summaries) will be flagged in these listings. Patients who will not be included in the analysis population of any corresponding analysis or summary will be flagged.

In general, the data will be summarized by scheduled assessment (if applicable) within each treatment group. For continuous variables, the summary statistics will include the mean, standard deviation, standard error, median, lower quartile, upper quartile, minimum, and maximum. Minimums

and maximums will be expressed using the level of precision in which the variable was collected. All other statistics will be rounded, using an additional decimal point. For discrete variables, summaries will include the frequency and percent in each category. Percentages will be rounded to one decimal point. For all inferential analyses and descriptive comparisons, p-values will be rounded to four decimal points. Values less than 0.0001 will be denoted as "<.0001", and values greater than 0.9999 will be denoted as ">.9999". Whenever practical, categories of discrete variables will be ordered and labeled as they appear in the CRF, and all categories represented on the CRF will be included in summaries, even when they do not apply to any patients in the study.

9.1 Study Population

All study population analyses will only be performed on the "*m*ITT" populations (see Section 6) for the individual studies. For the purposes of describing the random imbalance between the treatment groups, p-values from Fisher's Exact Test (for discrete variables) or Wilcoxon Rank Sum Test (for continuous variables) will be included on summaries, but are not intended to be used to test formal hypotheses. For these comparisons, missing or unknown values will be excluded from the calculations.

9.1.1 Patient Accountability

1. Listing of All Patients
2. Listing of Patient Accountability
3. Summary of Patient Accountability
4. Listing of Analysis Population Information
5. Summary of Analysis Population Information
6. Listing of Randomization Information
7. Summary of Randomization Information
8. Listing of Patient Completion/Discontinuation Information
9. Summary of Patient Completion/Discontinuation Information

A listing of all patients included in the report, sorted by patient number, will be provided as an aid to the reviewer. This listing will include investigator site number and treatment group.

The listing of patient accountability will include date of randomization, whether the patient received study drug, dates and times of first dose and final dose of study drug (as calculated from the infusion record), date patient completed or discontinued from study, and manner of normal completion or reason for premature discontinuation. Whether patients received study drug, whether patients completed the Week 1, Week 6 and Week 12 assessment, and normal completion versus premature discontinuation status will be summarized. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

Information regarding whether each patient is included in each analysis population (see Section 6) will be listed. If a patient is not included in a particular analysis population, the reason for exclusion will be noted on the listing. Also noted on the listing will be any modifications applicable to the patient for each population (e.g., randomized vs. actual treatment groups, treatment cross-over dates, etc.). The summary will include the frequency and percentage of all patients randomized into each treatment group included in each analysis population. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

All information used in the random assignment of patients to treatment group (from the central randomization database) will be listed, including date of randomization, treatment numbers, etiology of disease, exercise category at baseline, and vasodilator use at baseline ("yes" vs. "no"). For observations where any stratification information has been corrected, both the original and corrected information will be listed. Etiology of disease, exercise category at baseline, and vasodilator use at baseline will be summarized. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

All completion or discontinuation information will be listed, including date of patient completed or discontinued from study, manner of normal completion

or reason for premature discontinuation, whether the patient died during the study, the date and cause of death (if any), whether the patient received a transplant during the study, the date and type of transplant (if any), whether the patient will enter a continuation study, and whether the clinical care team remained blinded during the study. Manner of normal completion or reason for premature discontinuation, whether the patient died during the study, whether the patient received a transplant during the study, whether the patient will enter a continuation study, and whether the clinical care team remained blinded during the study will be summarized. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

Further analyses on premature discontinuations, deaths and transplantations are described in Section 9.2.2.3.

9.1.2 Protocol Deviations

1. Listing of Exceptions to Inclusion and Exclusion Criteria
2. Summary of Exceptions to Inclusion and Exclusion Criteria
3. Listing of Major Protocol Violations
4. Summary of Major Protocol Violations

Patients whose inclusion or exclusion criteria were either not all met or not all answered will be listed, along with a list of each criterion that is not met or answered. If a sufficient number of such exceptions occur, then the compliance to each criterion will be summarized. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

Each major protocol violation will be listed for all patients. A major protocol violation is defined as:

1) Receiving the wrong study drug (i.e., study drug to which patient was not randomized) for any part of the treatment period

2) Crossing over to the alternative study drug during the treatment period

3) Violation of inclusion criteria 3 and 6 (values on p. 14 of the CRF will be used to verify; PCWPm will not be used as the basis for violation)

4) Violations of exclusion criteria 7, 9, 10, 11, and 12

5) Use of any prostaglandins or their analogues for the treatment of pulmonary hypertension (as collected on the "Concomitant PHT Medications" pages [pp. 50.*] of the CRF) within seven days prior to the Week 12 exercise test.

6) Chronic concomitant use (use during at least 5 consecutive days during dosing period) of intravenous or inhaled medications to treat pulmonary hypertension (as collected on the "Concomitant PHT Medications" pages [pp. 50.*] of the CRF)

7) Other protocol violations may be considered on an individual patient basis prior to unblinding

If a sufficient number of such violations occur, the frequency and percentage of all patients in each treatment group with a major protocol violation, and the number of patients with each category of violation listed above will be presented. This summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

9.1.3 Other Descriptions of Study Population

9.1.3.1 Demographics and PHT History

1. Listing of Demographic Data
2. Summary of Demographic Data
3. Listing of PHT History
4. Summary of PHT History

All demographic data will be listed for all patients, including date of birth, age at randomization, race, sex, and childbearing potential (females only). Age, age category (<16, 16 - 64, and >64 years), race, and sex will be summarized. Childbearing potential will be summarized for all females. The summary will include p-values (two-sided) from Fisher's Exact Test (for

race, sex, and childbearing potential) or Wilcoxon Rank Sum Test (for age) comparing treatment groups.

Information regarding patients' PHT history will be listed, including date of initial PHT diagnosis, months since PHT diagnosis relative to date of randomization, current PHT diagnosis, current PHT NYHA class, and length of time (in months) at this classification. Current PHT diagnosis and current PHT NYHA class will be summarized. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

9.1.3.2 Medical History

1. Listing of Medical History
2. Summary of Medical History

All medical history conditions that were experienced either in the past or present at screen, or for which no answer was given, will be listed for all patients, along with any comments describing them. If a patient had no such conditions, this will be indicated on the listing. The summary will include frequency and percentage of patients in each treatment group experiencing each of the 16 predefined conditions in the past and the frequency and percentage of patients in each treatment group for whom each condition is present at screen. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

9.1.3.3 Complications of PHT

1. Listing of Complications of PHT
2. Summary of Complications of PHT

All complications of PHT that were experienced either in the past or present at screen, or for which the status was unknown, will be listed for all patients. If a patient had no such complications, this will be indicated on the listing. The summary will include frequency and percentage of patients in each treatment group experiencing each of the 45 predefined complications in the past and the frequency and percentage of patients in each treatment group for

whom each complication is present at screen. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

9.1.3.4 Physical Examinations and Baseline Vital Signs

1. Listing of Physical Examinations
2. Summary of Physical Examinations
3. Listing of Baseline Vital Signs
4. Summary of Baseline Vital Signs

The region/body system of all physical examination abnormalities, or regions/body systems for which an assessment was not available, will be listed for all patients, along with any comments on the abnormalities. If a patient had no such complications, this will be indicated on the listing. The summary will include frequency and percentage of patients in each treatment group with abnormalities present in each of the 13-regions/body systems. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

The listing of baseline vital signs will include assessment date, study day, weight (kg), height (cm), BSA (m^2), body temperature (in °C), pulse (beats/min), systolic and diastolic blood pressure (mm Hg), and respiration rate (breaths/min). Weight, height, BSA, body temperature, pulse, systolic and diastolic blood pressure, and respiration rate will be summarized numerically. The summary will include p-values (two-sided) from Wilcoxon Rank Sum Test comparing treatment groups.

9.1.3.5 Concomitant Therapy

9.1.3.5.1 Concomitant Medications

1. Listing of the Correspondence between Therapeutic Classes and Generic Drug Terms for All Concomitant Medications
2. Listing of Concomitant PHT Medications
3. Summary of Concomitant PHT Medications by Generic Drug Term
4. Summary of Concomitant PHT Medications by Therapeutic Class

5. Listing of Subcutaneous Infusion Site Concomitant Medications
6. Summary of Subcutaneous Infusion Site Concomitant Medications by Generic Drug Term
7. Summary of Subcutaneous Infusion Site Concomitant Medications by Therapeutic Class
8. Listing of Other Concomitant Medications
9. Summary of Other Concomitant Medications by Generic Drug Term
10. Summary of Other Concomitant Medications by Therapeutic Class

All medications specified on the CRF will be mapped to a generic drug term using a medication dictionary provided by the CRO providing data management services for these studies. Each generic term will then be mapped to the appropriate ATC code(s), which hierarchically characterize the drug's therapeutic class, based on a WHO classification system. For each type of concomitant medication ("PHT", "Subcutaneous Infusion Site", and "Other"), all unique ATC Level 2 or 3 Classifications will be listed, along with all corresponding unique generic drug terms.

The generic name and raw text of all concomitant PHT medications will be listed for all patients. This listing will include the total daily dose, units, route, date started (or indication that drug was ongoing at start of study), date discontinued (or indication that drug was ongoing at end of study), reason for the change, and whether the medication was taken to treat an AE. If a patient received no PHT medications, this will be indicated on the listing. One summary will include the frequency and percentage of patients in each treatment group receiving each drug (by generic term). Another summary will include the frequency and percentage of patients in each treatment group receiving one or more drugs from each unique therapeutic class (ATC Level 2 or 3 Classification). The summaries will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

The generic name and raw text of all subcutaneous infusion site concomitant medications will be listed for all patients. This listing will include the dose, units, route, frequency, date started, date discontinued (or indication that drug was ongoing at end of study), and overall change in severity of symptoms at the infusion site after adding this medication. If a patient received no such

medications, this will be indicated on the listing. One summary will include the frequency and percentage of patients in each treatment group receiving each drug (by generic term). Another summary will include the frequency and percentage of patients in each treatment group receiving one or more drugs from each unique therapeutic class (ATC Level 2 or 3 Classification). The summaries will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

The generic name and raw text of all other concomitant medications will be listed for all patients. This listing will include the date drug was first taken during study, and whether the medication was taken to treat an AE. If a patient received no such medications, this will be indicated on the listing. One summary will include the frequency and percentage of patients in each treatment group receiving each drug (by generic term). Another summary will include the frequency and percentage of patients in each treatment group receiving one or more drugs from each unique therapeutic class (ATC Level 2 or 3 Classification). The summaries will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

9.1.3.5.2 Concomitant Procedures

1. Listing of Concomitant Procedures
2. Summary of Concomitant Procedures

All concomitant procedures will be listed for all patients. This listing will include the date of the procedure, reason for the procedure, and whether the procedure was used to treat an AE. If a patient received no such procedures, this will be indicated on the listing. The summary will include the frequency and percentage of patients in each treatment group undergoing one or more concomitant procedures during the study, and the frequency and percentage of patients in each treatment group undergoing one or more procedures to treat an AE. The summary will include p-values (two-sided) from Fisher's Exact Test comparing treatment groups.

9.2 Efficacy Analyses

Except where otherwise noted, all efficacy analyses will only be performed on the "*m*ITT" populations (see Section 6) for the individual studies. If it is decided that the primary analysis is significant only for the pooled studies (see Section 8.1), then various analyses on principal reinforcing and secondary endpoints may also be performed on the "Pooled *m*ITT" population. If it is decided that the primary analysis is significant only for the subset of patients with PPH from the pooled studies (see Section 8.1), then various analyses on primary reinforcing and secondary endpoints may also be performed on the "Pooled *m*ITT PPH" population.

9.2.1 Primary Efficacy Endpoint: Exercise Capacity

1. Listing of Six-Minute Walk Exercise Test Data
2. Summary of Six-Minute Walk Distance over Time
3. Summary of Six-Minute Walk Changes from Baseline at Week 12 by Sex
4. Summary of Six-Minute Walk Changes from Baseline at Week 12 by Race
5. Summary of Six-Minute Walk Changes from Baseline at Week 12 by Age
6. Summary of Six-Minute Walk Changes from Baseline at Week 12 by Baseline Exercise
7. Summary of Six-Minute Walk Changes from Baseline at Week 12 by NYHA Class
8. Summary of Six-Minute Walk Changes from Baseline at Week 12 by Etiology of PHT
9. Summary of the Comparison of Six-Minute Walk Distances at Week 12
10. Summary of the Effect of Various Additional Covariates on the Comparison of Six-Minute Walk Distances at Week 12
11. Summary of the Comparison of Six-Minute Walk Distances at Week 12, Censored at the Time of Premature Discontinuation
12. Summary of the Comparison of Six-Minute Walk Distances at Week 12, Ignoring Center

13. Summary of the Comparison of Six-Minute Walk Distances at Week 12, Treating Chronic Use of New Concomitant PHT Medication as a Treatment Failure
14. Summary of the Comparison of Six-Minute Walk Distances at Week 12, Treating Concomitant Steroid Use as a Covariate
15. Summary of the Comparison of Six-Minute Walk Distances at Week 1
16. Summary of the Comparison of Six-Minute Walk Distances at Week 6

All six-minute walk exercise test data will be listed for all patients. For each patient, this listing will include the etiology of PHT (both original and corrected if it has been corrected since randomization), baseline exercise category (both original and corrected if it has been corrected since randomization), baseline vasodilator use (both original and corrected if it has been corrected since randomization), steroid use to treat PHT at baseline. Subjects not included in the "Per-Protocol" population will be flagged. For each assessment, the listing will include whether the patient attempted the exercise test, reason for not attempting test (if any), total distance walked (in meters), time started, time stopped, duration of test, whether patient walked the entire six minutes, and reason for shortened walk duration (if any). Distances that will be excluded from any of the analyses (for reasons described in Section 6 and Section 8.3) will be flagged.

The six-minute walk distances at baseline, Week 1, Week 6, and Week 12, and the changes from baseline at Week 1, Week 6, and Week 12 will be summarized for the individual and pooled "*m*ITT" populations, and the pooled "*m*ITT PPH" population. Baseline values will be compared using Wilcoxon Rank Sum Test, and the resulting two-sided p-values will be displayed on the summary. The changes from baseline at Week 12 will also be summarized by sex ("Male" and "Female"), race ("Caucasian", "Black", and "Other), age (<16, 16 – 64, and >64 years), baseline exercise (as used for randomization), NYHA Class ("II", "III", and "IV"), and etiology of PAH ("PPH" and "Other"). Missing values will be ignored for these descriptions.

Six-minute walk distances at Week 12 will be compared between treatment groups using nonparametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test[1,2,3]. A Cochran-Mantel Haenszel

mean score statistic will be used on the standardized mid-ranks (i.e., overall rank divided by the number of ranks + 1, or "modified ridit" scores) of the residuals from an ordinary least squares regression. This methodology will be carried out as follows:

1) An ordinary least squares regression will be fit to the protocol observed values of distance walked at Week 1, Week 6, and Week 12, as a function of distance walked at baseline, center, vasodilator use at baseline, etiology of pulmonary hypertension, and use of steroid therapy to treat PHT at baseline (see Section 8.2 for a detailed discussion of the covariates).

2) Standardized mid-ranks (or "modified ridit" scores) of the standardized residuals from this regression will be calculated.

3) As specified in Section 8.3, the standardized mid-rank from the last observation will be carried forward for missing values at Week 12, and failures at Week 12 will be assigned standardized mid-ranks of zero.

4) Standardized mid-ranks will be re-calculated.

5) A Cochran-Mantel Haenszel mean score statistic and p-value will be calculated, using the NOPRINT, CMH2 and SCORES=TABLE options of the TABLES statement of the FREQ procedure of SAS, comparing the Week 12 standardized mid-ranks between the treatment groups, adjusting for the stratification groupings that were used at randomization. The actual stratification used to randomize the patient will be used for the "*p*ITT" population, and stratification based on corrected information will be used for the "*m*ITT" and "Per-Protocol" populations.

A comparison between treatment groups of six-minute walk distances at Week 12 for the "*m*ITT" population, using this nonparametric approach, is the primary analysis for these studies. See Section 8.1 for a discussion of how the results from the individual and combined studies will be evaluated.

The results of the nonparametric approach will be presented for the individual and pooled "*m*ITT", "*p*ITT", and "Per-Protocol" populations, and the pooled

"*m*ITT PPH", "*p*ITT PPH", and "Per-Protocol PPH" populations. This summary will include the sample size, median, quartiles, minimum, and maximum distance walked within each population and treatment group, where failures at Week 12 will be assigned values of zero and the last observation will be carried forward for missing or censored values (see Section 8.3 for handling of missing data). The summary will also include the two-sided p-value from the treatment comparison within each population.

As a secondary (confirmatory) approach, six-minute walk distances at Week 12 (see Section 8.3 for handling of missing data) will be compared between treatment groups using parametric ANCOVA, adjusting for distance walked at baseline, center, vasodilator use at baseline, etiology of pulmonary hypertension, and use of steroid therapies at baseline (see Section 8.2 for a detailed discussion of the covariates). Further models will be fit, including each treatment by covariate interaction term (one at a time), to examine whether treatment effect is related to any of the covariates.

Model estimates associated with the treatment effect from the parametric ANCOVA models without treatment interaction terms will be presented for the individual and pooled "*m*ITT", "*p*ITT", and "Per-Protocol" populations, and the pooled "*m*ITT PPH", "*p*ITT PPH", and "Per-Protocol PPH" populations. This summary will include the standard error and p-value (Type III, two-sided) for the treatment term. The p-values (Type III, two-sided) from the overall tests of each interaction term will be presented, along with their associated degrees of freedom. The model estimates for treatment effects, their standard errors, and their p-values (Type III, two-sided) will be presented within subgroups corresponding to each interaction term with an overall p-value of less than 0.1000.

In order to explore the effects of various other covariates on the treatment comparisons, parametric ANCOVA models may be fit including sex, race, age, baseline hemodynamics, NYHA Class, specific etiology, groupings of geographic regions, and chronic concomitant use (use of drug at least 75% of the time during the dosing period) of vasodilators, anticoagulants, diuretics, and digoxin to treat pulmonary hypertension (as collected on the "Concomitant PHT Medications" pages [pp. 50.*] of the CRF), and chronic

concomitant use of analgesics (as collected on any of the concomitant medication pages [pp. 50.*, 51.*, 52.*] of the CRF; see Section 8.4 for definitions of these classes) as further covariates. Each covariate will be individually added to the original model, both with and without a treatment interaction term. Model estimates for each model will be presented, along with their standard errors and p-values (Type III, two-sided).

To support the robustness of the primary analysis (provided that the primary analysis yields significant results), the above nonparametric and parametric analyses will be repeated for the individual and pooled "*m*ITT" populations and the pooled "*m*ITT PPH" population using each of the following modifications:

1) Six-minute walk distances will be censored at the time of study discontinuation for any reason (by not having data after discontinuation included in the analysis). The last standardized rank before discontinuation will be carried forward for nonparametric analyses and the last observation before discontinuation will be carried forward for parametric analyses.

2) Center will <u>not</u> be included as a covariate.

3) Patients who begin prolonged treatment (for at least 10 days during the dosing period) with new classes of pulmonary hypertension medications (relevant classes are "Vasodilators", "Diuretics", "Digoxin", and "Oxygen"; see Section 8.4 for definitions of these classes based on medications listed on the "Concomitant PHT Medications" pages [pp. 50.*] of the CRF) during the study will be considered treatment failures. In addition, patients who begin rescue therapy with intravenous inotropes (e.g., dobutamine or dopamine) will be considered treatment failures. Therefore, the lowest standardized rank will be used for nonparametric analyses and a walk distance of zero will be used for parametric analyses. This analysis is considered to be favorable to study drug.

4) Chronic use (use for at least 75% of the time during the dosing period) of oral (or other non-topical) steroid therapies (see Section 8.4 for

definitions of relevant steroid therapies, based on medications listed on the "Concomitant PHT Medications" or "Subcutaneous Infusion Site Concomitant Medications" pages [pp. 50.*, 51.*] of the CRF) during the 12-week treatment period will be treated as a dichotomous covariate.

5) Only data through the Week 1 exercise test assessment will be used.

6) Only data through the Week 6 exercise test assessment will be used.

As a possible further approach to examine how the primary efficacy endpoint results are influenced by patients for whom the use of steroids or vasodilators changes during the study, analyses may be applied with assigned rankings that account for steroid or vasodilator use changes, and these ranks may be compared between treatment groups using nonparametric ANCOVA.

9.2.2 Principal Reinforcing Endpoints

9.2.2.1 Signs and Symptoms of PHT

1. Listing of Signs and Symptoms of PHT
2. Summary of Signs and Symptoms of PHT over Time
3. Summary of Changes from Baseline in Signs and Symptoms of PHT

All assessments of signs and symptoms of PHT will be listed for all patients. This listing will include whether each sign or symptom was "absent", "present" or "unknown" during the assessment, and all relevant details collected for the particular sign or symptom. The status of each sign and symptom ("absent", "present" or "unknown") at each scheduled assessment will be summarized. For the signs and symptoms for which additional details are collected, the details will be categorically summarized for patients for whom the sign or symptom was present. The presence of each sign and symptom at baseline will be compared between treatment groups using Fisher's Exact Test, and the resulting two-sided p-values will be included on the summary. Observations for which a sign or symptom's status is unknown will be excluded from this comparison.

In order to assess overall change from baseline in the signs and symptoms of PHT, for each post-baseline assessment, a "1" will be assigned for each sign and symptom that is "present" at the assessment and was "absent" at baseline, a "-1" will be assigned for each sign and symptom that is "absent" at the assessment and was "present" at baseline, and a "0" will be assigned otherwise. An overall change score at each post-baseline assessment will then be calculated by summing these values over all signs and symptoms. A change score will not be calculated if fewer than 8 of the 16 signs and symptoms were evaluated at a given assessment. These overall changes scores at Weeks 1, 6, and 12 will be summarized numerically. The overall change scores will be compared between treatment groups using Wilcoxon Rank Sum Test. The resulting two-sided p-values will be displayed on the summary.

9.2.2.2 Dyspnea-Fatigue Index

1. Listing of Dyspnea-Fatigue Index
2. Summary of Dyspnea-Fatigue Index
3. Summary of Change from Baseline in Dyspnea-Fatigue Index

The Dyspnea-Fatigue Index is comprised of three components, each with a scale of 0 to 4. It is calculated as the sum of these components, and ranges from 0 (for the worst condition) to 12 (for the best condition).

The Dyspnea-Fatigue Indices at all assessments will be listed for all patients, along with the individual "Magnitude of task", "Magnitude of pace", and "Functional impairment" component scores. For each post-baseline assessment, the change from baseline in Dyspnea-Fatigue Index will also be included on the listing. The Dyspnea-Fatigue Indices at baseline, Week 1, Week 6, and Week 12, and the changes from baseline at Week 1, Week 6, and Week 12 will be summarized numerically. The summary of the raw values will include a categorical summary of each of the three components of the Dyspnea-Fatigue Index at each time point. Baseline values will be compared using Wilcoxon Rank Sum Test, and the resulting two-sided p-values will be displayed on the summary. The changes from baseline will be

compared between treatment groups using Wilcoxon Rank Sum Test. The resulting two-sided p-values will be displayed on the summary of changes from baseline.

9.2.2.3 Mortality, Transplantation, and Discontinuation of Study Drug

1. Listing of Deaths, Transplantations, and Discontinuation of Study Drug Due to Clinical Deterioration
2. Summary of Mortality, Transplantation, and Discontinuation of Study Drug Due to Clinical Deterioration
3. Plot of the Kaplan-Meier Estimates of the Time to Death, Transplantation, or Discontinuation of Study Drug due to Clinical Deterioration
4. Plot of the Kaplan-Meier Estimates of the Time to Death or Discontinuation of Study Drug due to Clinical Deterioration Censored at the Time of Transplantation or Premature Discontinuation

Occurrence of death, transplantation, and study drug discontinuation due to clinical deterioration during 12-week study period will be listed for all patients, along with the date and study day of each such event. If a patient received study drug for the entire 12-week study period, this will be indicated on the listing. If a patient prematurely discontinued from the study due to withdrawal of consent, protocol violation, loss to follow-up, or an AE, then the date of discontinuation and reason for discontinuation will be included on the listing.

Occurrence of mortality, mortality or transplantation, and mortality, transplantation or discontinuation of study drug due to clinical deterioration will be summarized. This summary will include odds-ratios and differences in rates between the treatment groups for each of these events, along with 95% confidence intervals on each.

The time (in days) from randomization to death, transplantation, or discontinuation of study drug due to clinical deterioration will be calculated. If a patient prematurely discontinues from the study due to withdrawal of consent, protocol violation, loss to follow-up, or an AE, then this time will be

censored at the time of discontinuation from the study, unless a death is reported before Week 12. Patients receiving study drug for the full 12-week study period will be censored at 12 weeks. Kaplan-Meier estimates will then be calculated, and displayed graphically. The two-sided p-value from a Wilcoxon Rank Scores Test comparing treatment groups will be displayed on the plot. This analysis will be repeated, censoring the time to death or discontinuation of study drug due to clinical deterioration at the time of transplantation or premature discontinuation from the study, regardless of whether the patient subsequently dies before Week 12.

9.2.3 Secondary Efficacy Endpoints

9.2.3.1 Borg Dyspnea Score

4. Listing of Borg Dyspnea Score
5. Summary of Borg Dyspnea Score
6. Summary of Change from Baseline in Borg Dyspnea Score

The Borg Dyspnea Score at all assessments will be listed for all patients. For each post-baseline assessment, the change from baseline in Borg Dyspnea Score will also be included on the listing. The Borg Dyspnea Score at baseline, Week 1, Week 6, and Week 12, and the changes from baseline at Week 1, Week 6, and Week 12 will be summarized. Baseline values will be compared using Wilcoxon Rank Sum Test, and the resulting two-sided p-values will be displayed on the summary. The changes from baseline will be compared between treatment groups using Wilcoxon Rank Sum Test. The resulting two-sided p-values will be displayed on the summary of changes from baseline.

9.2.3.2 Hemodynamics and Oxygen Saturation

1. Listing of Hemodynamic and Oxygen Saturation Measurements
2. Summary of Hemodynamic and Oxygen Saturation Measurements

3. Summary of Changes from Baseline in Hemodynamic and Oxygen Saturation Measurements

The following hemodynamic and oxygen saturation measurements were collected (or can be derived) at baseline and Week 12:

Parameter	**Abbrev**	**Units**
Heart Rate	HR	beats/bin
Respiration Rate	(none)	breaths/min
Temperature*	(none)	°F
Systemic Arterial Pressure – systolic	SAPs	mm Hg
Systemic Arterial Pressure – diastoloic	SAPd	mm Hg
Systemic Arterial Pressure – mean	SAPm	mm Hg
Pulmonary Arterial Pressure – systolic	PAPs	mm Hg
Pulmonary Arterial Pressure – diastolic	PAPd	mm Hg
Pulmonary Arterial Pressure – mean	PAPm	mm Hg
Right Atrial Pressure	RAPm	mm Hg
Pulmonary Capillary Wedge Pressure	PCWPm	mm Hg
Transcutaneous Oxygen Saturation (or Arterial Saturation)	T_cO_2 S_aO_2	%
Mixed Venous Saturation	S_vO_2	%
Cardiac Output (Thermodilution) -or- Cardiac Output (Fick)**	CO	L/min
FiO_2 -or-	FiO_2	%
Oxygen Delivery Rate***	O_2	L/min
Pulmonary Arterial Saturation****	PAS	%
Pulmonary Venous Saturation****	PVS	%
Measured Oxygen Consumption****	(none)	mL/min
Cardiac Index*	CI	L/min/m^2
Stroke Volume*	SV	mL/beat
Stroke Index*	SI	mL/beat/m^2
Systemic Vascular Resistance*	SVR	mm Hg/(L/min)
Systemic Vascular Resistance Index*	SVRI	mm Hg/(L/min/m^2)
Total Pulmonary Resistance*	TPR	mm Hg/(L/min)
Total Pulmonary Resistance Index*	TPRI	mm Hg/(L/min/m^2)
Pulmonary Vascular Resistance*	PVR	mm Hg/(L/min)
Pulmonary Vascular Resistance Index*	PVRI	mm Hg/(L/min/m^2)

* see Section 8.4 for derivation
** Fick required for shunt patients
*** collected for patients receiving oxygen at time of catheterization
**** collected for patients with unrepaired congenital systemic-to-pulmonary shunt or atrial septostomy

Once the appropriate derivations and unit conversions have been done, all of the above information will be listed for all patients and assessments. The listing will include whether patients were receiving oxygen at the time of catheterization, and whether patients had an unrepaired congenital systemic-to-pulmonary shunt or atrial septostomy.

Values of all parameters at baseline and Week 12, and their corresponding changes from baseline at Week 12 will be summarized. Changes from baseline in HR, RAPm, CI, PAPm, PVRI, SAPm, SVRI, and S_vO_2 at Week 12 will be compared between treatment groups using a parametric ANCOVA model adjusting for baseline value. The resulting p-values (Type III, two-sided) corresponding to treatment effect will be included on the summary of changes from baseline. Model estimates associated with the treatment effect from the parametric ANCOVA models without treatment interaction terms will be presented, along with the standard error and p-value (Type III, two-sided).

9.3 Quality of Life Analyses

1. Listing of Quality of Life Data
2. Summary of Quality of Life
3. Summary of Changes from Baseline in Quality of Life

Patients' quality of life will be assessed at baseline, Week 6, and Week 12 using the 21-question "Living with Right Heart Failure" questionnaire. Each response corresponds to a numeric value between 0 and 5. For each assessment, a global quality of life score, physical dimension score, and emotional dimension score will be calculated as follows:

To calculate:	Sum the responses to Questions:	Divide the sum by the number of questions that were answered, and multiply by:
Global QoL Score	1-21	21
Physical Dimension Score	2-7, 12, 13	8
Emotional Dimension Score	17-21	5

Note: In order to calculate a score, >50% of the questions relating to that score must be answered.

The response to each question, the physical dimension score, the emotional dimension score, and the global quality of life score will be listed for all patients and assessments. The physical dimension score, the emotional dimension score, and the global quality of life score at baseline, Week 6, and Week 12, and their changes from baseline at Week 6 and Week 12 will be summarized. Baseline values will be compared using Wilcoxon Rank Sum Test, and the resulting two-sided p-values will be displayed on the summary. The changes from baseline will be compared between treatment groups using Wilcoxon Rank Sum Test. The resulting two-sided p-values will be displayed on the summary of changes from baseline.

9.4 Safety Analyses

All safety analyses will be performed only on the "Safety" populations (see Section 6) for the individual studies. Safety analyses on pooled data will be handled separately in the ISS section of the NDA.

9.4.1 Extent of Exposure

1. Listing of the Study Drug Infusion Record for Dose Optimization
2. Listing of the Outpatient Study Drug Infusion Record
3. Summary of the Study Drug Infusion Record
4. Summary of the Changes in Study Drug Dosing
5. Summary of Study Drug Dosing at Early Discontinuation of Study Drug

For all patients, each actual dose (ng/kg/min), infusion rate (units/hour), and study drug concentration recorded on the dose optimization page of the CRF will be listed, along with the date, time, and time (hours) relative to the start of infusion that the dose was started and stopped, and any reason codes for dose reductions or discontinuations. Additionally, each new dose, infusion rate, and study drug concentration recorded on the outpatient drug infusion record will be listed, along with the date, time, and study day that the dose was changed, and the reason(s) for the change.

The initial dose (ng/kg/min) and the doses at the end of Weeks 1 through 12 will be summarized. In addition, the number of dosing increases, decreases,

and total number dosing of changes per patient during Week 1, Weeks 1-4, Weeks 5-8, and Weeks 9-12 will be numerically and categorically summarized.

The duration of dosing (in weeks) and study drug dose (ng/kg/min) at the time of discontinuation will be summarized for all patients discontinuing study drug before the end of the 12-week dosing period.

9.4.2 Adverse Events

1. Listing of the Correspondence of Raw Adverse Event Terms to Preferred Terms and Body Systems
2. Listing of All Adverse Events
3. Summary of Adverse Events by Seriousness and Causality
4. Summary of Adverse Events by Intensity and Causality
5. Summary of Frequently Reported Adverse Events
6. Summary of Adverse Events by Lowest Dose of Study Drug at Onset
7. Summary of Dose Limiting Adverse Events by Lowest Dose of Study Drug at Onset
8. Summary of Adverse Events After Discontinuation of Study Drug

To facilitate summarization, COSTART codes will be used to map raw adverse event terms into more general preferred terms and body systems. The correspondence between the raw adverse event terms and the COSTART preferred terms and body systems will be listed.

All adverse events will be listed for all patients. The listing will include the date, time and study day of onset and cessation (or an indication that it was ongoing at the end of the study), seriousness, intensity, frequency, causality, action taken, comment, and the dose of the study drug (ng/kg/min) at the time of the start of the adverse event. If a patient did not experience an adverse event during the study, this will be indicated on this listing.

An adverse event is considered "treatment emergent" if it is not present during the screening or baseline phase or increases in either seriousness or intensity after the start of the treatment phase. The maximum seriousness and

intensity of each treatment emergent event for each patient will be summarized by causality. Frequently reported adverse events, defined as those observed in more than 3% of patients within a treatment group, will be summarized separately in order of overall decreasing frequency. These summaries will include one-sided p-values (favoring the placebo group) from Fisher's Exact Test comparing the incidence rates between the treatment groups. Values greater than 0.25 will be denoted as ">.2500".

The lowest study drug dose at which each patient experienced each type of treatment emergent adverse event and each type of treatment emergent adverse event that required a dose decrease or discontinuation will be calculated. These doses will be categorized into discrete intervals (initially >0-5, >5-10, >10-20, and >20 ng/kg/min), which may be modified, depending on the data. The frequency and percentage of patients in each treatment group experiencing each type of event at each dose category and overall will then be presented.

The frequency and percentage of patients in each treatment group experiencing each type of treatment emergent adverse event after discontinuation (temporary or permanent) of study drug (but before study drug is re-started) within the 12-week treatment period will be presented.

9.4.3 Deaths

1. Listing of Deaths
2. Summary of Mortality

All patients who died during the study will be listed, along with their date and study day of death, cause of death, and study drug dosage at the time of death.

Survival status in all patients and patients discontinuing the study for any reason will be summarized. The summary will include one-sided p-values (favoring the placebo group) from Fisher's Exact Test comparing only the overall mortality rates between the treatment groups. A values greater than 0.25 will be denoted as ">.2500".

9.4.4 Clinical Laboratory Evaluations

Blood samples will be taken at baseline and Week 12, and sent to a central laboratory for evaluation of clinical chemistry and hematology. Urine samples will also be collected at baseline and Week 12, and sent to a central laboratory for urinalysis. Local labs will be used to evaluate coagulation times at baseline and Week 12.

9.4.4.1 Clinical Chemistry

1. Listing of Clinical Chemistry Data
2. Summary of Clinical Chemistry Data
3. Summary of Clinical Chemistry Changes from Baseline
4. Summary of Clinical Chemistry Shifts from Baseline
5. Plot of Clinical Chemistry Shifts from Baseline

The following clinical chemistry parameters will evaluated by the central laboratory:

Parameter	**Units**
Sodium	mmol/L
Potassium	mmol/L
Chloride	mmol/L
Bicarbonate	mmol/L
Calcium	mg/dL
Albumin	g/dL
BUN	mg/dL
Total Bilirubin	mg/dL
Alkaline Phosphatase	IU/L
LDH	IU/L
ALT (SGPT)	IU/L
AST (SGOT)	IU/L
Creatinine	mg/dL

Values that are “high” or “low” with respect to the normal range provided by the central laboratory will be flagged with an “H” or an “L”. All parameters will be listed for all patients and assessments, along with their respective “high/low” flags.

Values of these parameters at baseline and Week 12, and their corresponding changes from baseline at Week 12 will be summarized. Changes from baseline of these measurements at Week 12 will be compared between treatment groups using Wilcoxon Rank Sum Tests, and the resulting one-sided p-values (favoring the placebo group) will be included on the summary of changes from baseline. Values greater than 0.25 will be denoted as ">.2500".

For each parameter, the frequency and percentage of patients within each treatment group who had "low", "normal", or "high" baseline values, then subsequently had "low", "normal", or "high" Week 12 values will be presented in a shift summary. In addition, baseline values will be plotted against Week 12 values for each parameter, separately for each treatment group. These plots will have the central laboratory's normal range indicated on each axis.

9.4.4.2 Hematology

1. Listing of Hematology Data
2. Summary of Hematology Data
3. Summary of Hematology Changes from Baseline
4. Summary of Hematology Shifts from Baseline
5. Plot of Hematology Shifts from Baseline

The following hematology parameters were evaluated by the central laboratory:

Parameter	**Units**
RBC Count	10^{12}/L
Hemoglobin	g/dL
Hematocrit	%
Platelet Count	10^{9}/L
WBC Count	10^{9}/L
Neutrophils	%
Lymphocytes	%
Monocytes	%
Eosinophils	%
Basophils	%
Bands	%

Values that are "high" or "low" with respect to the normal range provided by the central laboratory will be flagged with an "H" or an "L". All parameters will be listed for all patients and assessments, along with their respective "high/low" flags.

Values of these parameters at baseline and Week 12, and their corresponding changes from baseline at Week 12 will be summarized. Changes from baseline of these measurements at Week 12 will be compared between treatment groups using Wilcoxon Rank Sum Tests, and the resulting one-sided p-values (favoring the placebo group) will be included on the summary of changes from baseline. Values greater than 0.25 will be denoted as ">.2500".

For each parameter, the frequency and percentage of patients within each treatment group who had "low", "normal", or "high" baseline values, then subsequently had "low", "normal", or "high" Week 12 values will be presented in a shift summary. In addition, baseline values will be plotted against Week 12 values for each parameter, separately for each treatment group. These plots will have the central laboratory's normal range indicated on each axis.

9.4.4.3 Coagulation Times

1. Listing of Prothrombin Times
2. Summary of Prothrombin Times

Prothrombin times and/or prothrombin INR values will be listed for all patients and assessments. This listing will include the normal range or control value for the prothrombin time, whether the results were "normal" or "abnormal", and the comment for abnormal results.

Prothrombin time and prothrombin INR values at baseline and Week 12, and changes from baseline at Week 12 will be summarized. This summary will also include the frequency and percentage of patients in each treatment group who had a "normal" result at baseline and an "abnormal" result at Week 12.

9.4.4.4 Urinalysis

1. Listing of Urinalysis Results
2. Summary of Urinalysis Results

All urinalysis information will be listed for all patients and assessments. The amount of protein and blood in the urine will be categorically summarized. The frequency and percentage of patients in each treatment group who had a normal protein or blood screen at baseline and an abnormal result at Week 12 will be included on the summary.

9.4.5 Other Safety Measures

9.4.5.1 12-Lead ECG

1. Listing of 12-Lead ECG Results
2. Summary of 12-Lead ECG Results

All ECG assessments will be listed for all patients. This listing will include the heart rate, QT interval, PR interval, QRS duration, QRS axes, whether abnormalities were present, and details and comments on any abnormalities. The ECG results (normal vs. abnormalities present) at baseline and Week 12 will be summarized. This summary will also include the frequency and percentage of patients within each treatment group who had a normal result at baseline and abnormalities present at Week 12, and the frequency and percentage of patients who had any abnormalities present at baseline and a normal result at Week 12. The frequency and percentage of patients in each treatment group who had any specific abnormalities at Week 12 that were not present at baseline will also be included on the summary.

9.4.5.2 Vital Signs (during dose optimization)

1. Listing of Vital Signs During Dose Optimization
2. Summary of Vital Signs During Dose Optimization

All vital sign assessments collected during dose optimization will be listed for all patients. The listing will include the date, time, and time (in hours) relative to the most recent increase in study drug dose of each assessment, systolic and diastolic blood pressure, pulse, and respiration rate. Systolic and diastolic blood pressure, pulse, and respiration rate will be summarized for all scheduled assessments.

9.4.5.3 Subcutaneous Infusion Site Symptoms

1. Listing of Infusion Site Symptoms During Dose Optimization
2. Listing of Chronic Subcutaneous Infusion Site Symptoms
3. Summary of Chronic Subcutaneous Infusion Site Symptoms

All infusion site symptoms documented during dose optimization will be listed for all patients. The listing will include the date, time, and study day of each assessment, whether treatment was administered for the symptom, and each specific symptom that was present on the day infusion was initiated, and then every day post initiation for four days. Details about each symptom will also be included on the listing.

All weekly assessments of chronic infusion site symptoms will be listed for all patients. The listing will include the intensity and comment for each symptom that was experienced. If a patient had no such symptoms, this will be indicated on the listing. If a treatment was administered for any infusion site symptoms, this will be indicated on the listing. The summary will include the frequency and percent of patients in each treatment group experiencing each of the four predefined symptoms during each of the 12 weeks of the dosing period.

9.4.5.4 Drug Delivery System Complications

1. Listing of Drug Delivery System Complications

All drug delivery system complications will be listed for all patients. The listing will include the type of complication, date, time and study day of onset and cessation, action taken, and whether the complication resulted in an

adverse event. If a patient had no such complications, this will be indicated on the listing.

9.5 Pharmacokinetic Analyses

Pharmacokinetic analyses will be described separately.

10 REFERENCES

1 Koch GG, Carr GJ, Amara IA, Stokes ME, and Uryniak TJ, Categorical data analysis, in *Statistical Methodology in the Pharmaceutical Sciences*, ed DA Berry, New York: Marcel Dekker Inc. 1990, 391-475.

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3 Stokes ME, Davis CS, and Koch GG, *Categorical Data Analysis Using the SAS System*, Cary, NC: SAS Institute Inc. 1995.

Appendix C : Remodulin™ P01:04/05 Combined Rank Analysis on 6-Minute Walk Distance and Borg Score

APPENDIX C: Combined Rank Analysis on 6-Minute Walk Distance and Borg Score

Six-minute walk distances and Borg scores at Week 12 were simultaneously compared between treatment groups using nonparametric analysis of covariance within the framework of the extended Cochran-Mantel-Haenszel test (analogous to the primary analysis methodology). This methodology was carried out as follows:

1) Standardized mid-ranks of 6-minute walk distances were calculated:
    i) An ordinary least squares regression was fit to the protocol observed values of distance walked at Week 1, Week 6, and Week 12, as a function of distance walked at baseline, center, vasodilator use at baseline, etiology of pulmonary hypertension.
    ii) Standardized mid-ranks (or "modified ridit" scores) of the standardized residuals from this regression were calculated.
    iii) Failures at Week 12 were assigned standardized mid-ranks of zero, and the standardized mid-rank from the last observation was carried forward for other missing values at Week 12.
    iv) Standardized mid-ranks were re-calculated.
2) Standardized mid-ranks of 6-minute walk Borg score changes from baseline were calculated:
    i) Changes from baseline in the protocol observed Borg scores at Week 1, Week 6, and Week 12 were calculated.
    ii) Standardized mid-ranks of these changes from baseline were calculated, and the resulting ranks were subtracted from one (since negative changes in Borg scores are favorable).
    iii) Failures at Week 12 were assigned standardized mid-ranks of zero, and the standardized mid-rank from the last observation was carried forward for other missing values at Week 12.
    iv) Standardized mid-ranks were re-calculated.
3) The standardized mid-ranks for distance and for Borg score were combined by calculating their arithmetic average.
4) Standardized mid-ranks of the resulting mean ranks were calculated.
5) A Cochran-Mantel Haenszel mean score statistic and p-value were calculated using the NOPRINT, CMH2 and SCORES=TABLE options of the TABLES statement of the FREQ procedure of SAS, comparing the combined standardized mid-ranks between the treatment groups, adjusting for the stratification groupings that were used at randomization (ignoring baseline walk category). These groupings were based on the corrected information as it appears in the CRF.

Reference

1. Rich, S. Primary Pulmonary Hypertension: Executive Summary from the World Symposium – Primary Pulmonary Hypertension, 1998. World Health Organization, 1998; 1-27.

PRIMARY PULMONARY HYPERTENSION

EXECUTIVE SUMMARY

FROM THE

World Symposium –
Primary Pulmonary Hypertension 1998

EVIAN, FRANCE
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co-sponsored by

The World Health Organization

edited by Stuart Rich, MD

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INTRODUCTION

Primary pulmonary hypertension is a rare condition, with an estimated prevalence of 1-2 per million people. Because the symptoms of PPH are nonspecific, and the physical findings can be subtle, the disease is often diagnosed in its later stages. The natural history of PPH is usually progressive and fatal.

In 1973, the World Health Organization sponsored an international meeting on primary pulmonary hypertension, spurned by the interest created by the sudden increase in patients with PPH who had used the anorexigen, aminorex fumarate. At that vanguard meeting, international experts reviewed and discussed the pathology, pathophysiology, epidemiology, and clinical features of PPH. The meeting also focused on defining areas of future research with the goal of providing a better understanding of the cause and discovering effective treatments for PPH.

The past 25 years has witnessed remarkable progress in the field of pulmonary hypertension. The pathology is now better defined and intricate pathobiologic mechanisms are becoming unfolded that explain many of the enigmatic features of PPH. Risk factors have been identified, and the genetics are being characterized. Advances in technology allow a better diagnosis and assessment of the disease severity. Important therapies are now available that have been shown to improve quality of life and survival.

On the 25th anniversary of this first meeting, clinical scientists from around the world gathered again to review and discuss the features of PPH, as well as the field of pulmonary arterial hypertension. Ironically, a recent epidemic of PPH associated with a new class of anorexigens has again heightened world interest. Like before, the merging of a variety of disciplines provided an opportunity for discussion and debate, leading to a better understanding of the pathology, pathobiology, risk factors, genetics, diagnosis and treatment of the disease. New drugs, such as epoprostenol, and surgical therapies, such as heart-lung transplant that were unavailable 25 years ago, are having an important impact on the prognosis.

This executive summary highlights key features of PPH and represents a consensus of the participants who contributed to this working meeting. It provides insights into our current understanding of PPH, with specific recommendations for current practice and future directions for research.

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THE PATHOLOGY OF PULMONARY HYPERTENSION

VASCULAR ABNORMALITIES

The pathology of the pulmonary vascular bed in pulmonary hypertension remains central to our understanding of clinical observations and pathobiologic mechanisms. The cellular and molecular features of the pathology continues to influence the clinical appraisal of the disease.

ENDOTHELIUM

The endothelium presents a challenge to the pathologist because of the marked heterogeneity in the endothelium of the pulmonary vascular bed. In addition, the relationship between the phenotype and function of the endothelial cell is not fully understood. There may also be discordance between the patient age and the apparent cell age of the endothelium.

The characteristics of the disease and the vulnerability of different phenotypes to a variety of insults may determine the nature and severity of endothelial changes that are observed. This makes our understanding of how modulating the chemical and physical environment alters the endothelium quite important. Immunocytochemistry and in situ hybridization has shown that endothelial cells have increased levels of Factor VIII antigen, the VEGF receptor, Kdr, endothelial nitric oxide synthase and endothelin-1. It is possible that these endothelial markers can be applied to diagnose early lesions.

It is not known at what stage during the evolution of PPH that endothelial cell proliferation occurs since it has not been consistently reported by all pathologists. Its presence, if confirmed, would suggest that a somatic mutation, rather than non-selective cell proliferation in response to injury, accounts for the growth advantage of endothelial cells in PPH.

SMOOTH MUSCLE CELLS

Heterogeneity exists in the smooth muscle cells and fibroblast populations. Like the endothelium, the relationships between phenotype and function need clarification. There needs to be emphasis on the synthesis of matrix components and the modulation of phenotype to degrade and synthesize specific components. Interconversion may occur between cell types (i.e., fibroblast to smooth muscle cell,

endothelium to smooth muscle cell), as well as the possibility of new vessel formation. With respect to the adventitial fibroblast, it manifests a peculiar response to physical stress in relation to matrix production. Finally, information from the study of normal vascular development and differentiation needs to be applied to the pathology of pulmonary hypertension.

In the large muscular and elastic arteries, smooth muscle cell hypertrophy and increased connective tissue and extracellular matrix is found. Dissolution of the elastic lamina is also a frequent finding. In the sub-endothelial or intimal layer, increased thickness may be the result of both recruitment and/or proliferation of smooth muscle-like cells. It is possible that precursor smooth muscle cells are in a continuous layer in the sub-endothelial layer along the entire pulmonary artery. These cells are similar to the pericytes that are responsible for the appearance of muscle in normally non-muscular arteries and that contribute to the intimal thickening in larger arteries.

The complexity of the remodeling in the media and adventitia is in part due to the presence of different smooth muscle cell types in several layers of the wall. Alterations in phenotype of the different layers of smooth muscle cells may contribute to the maintenance of PPH. The finding of a distinct smooth muscle cell type in the pulmonary artery needs further exploration. The phenotypes of smooth muscle cells are likely to have different functions and metabolic activity in each layer.

Extracellular Matrix

Alterations in the extracellular matrix secondary to proteolytic enzymes appear to contribute to the pathology in an important way. Matrix degrading enzymes can release mitogenically active growth factors that stimulate smooth muscle cell proliferation. In addition, elastase and matrix metalloproteinases can contribute to the up-regulation of the proliferation as well as the glycoprotein tenascin through a β-3 integrin-mediated transcriptional control mechanism. This could explain robust cellular proliferation in the presence of excess deposition of a tenascin rich matrix. The degradation of elastin has also been shown to stimulate up-regulation of the glycoprotein fibronectin which stimulates smooth muscle cell migration.

The Plexiform Lesion

The plexiform lesion remains a mystery. It is possible that it represents endothelial cells that are involved prominently in angiogenesis, perhaps akin to a neoplastic process. Morphologically they represent a mass of disorganized vessels with proliferating endothelial cells, smooth muscle cells, myofibroblasts and macrophages and arise from preexisting, presumably parent pulmonary arteries. Several studies have shown the involvement of growth factors that have been implicated in angiogenesis. Whether the plexiform lesion represents impaired proliferation or angiogenesis remains unclear.

PATHOLOGIC INTERPRETATION AND CLASSIFICATION OF PULMONARY HYPERTENSION

It is recommend that the previous pathological classification of pulmonary vascular disease be abandoned. It has been found to be too restrictive and the classes and grades do not correlate with the clinical and hemodynamic findings in a consistent prognostic fashion outside of congenital heart disease. Nor does the

graded classification system aid in clarifying the pathogenesis of the many causes of pulmonary vascular disease.

Rather than classifying the pathological abnormalities, we recommend the use of a new protocol designed to improve our understanding of the clinical picture, which is descriptive rather than prescriptive. We also encourage the application and interpretation of new histochemical and molecular biologic techniques. The pathologist is expected to interpret pathological findings in the light of the clinical and hemodynamic information, and to give guidance to the clinician by commenting on whether the findings are consistent with, or help explain, the clinical findings in light of our present understanding. The protocol should help ensure that the description of the findings be comprehensive, reproducible and be easy to follow by all pathologists.

The following structures should be examined and noted:

I. Vasculature

A. Vessels

Elastic, pre- and intra-acinar arteries, microvessels, post-acinar and intra-acinar veins, capillaries, lymphatics, and bronchial vessels. The vessel lumen should be commented on with respect to thrombi (recent or old) and abnormal cellular and matrix components.

B. Components

1. Endothelium/Intima
   (a) Cellular components (endothelial cells and smooth muscle cells)
   (b) Matrix (elastin, collagen, mucopolysaccarides)
2. Media
   (a) Pattern (eccentric or concentric)
   (b) Cellular components (smooth muscle and/or other cells)
   (c) Matrix
3. Adventitia
   (a) Cellular components (fibroblasts)
   (b) Matrix
4. Complex Vascular Lesions: Dilatation complexes, plexiform lesions, fibrinoid necrosis, arteritis, hemosiderosis, granulomas.
5. Inflammatory Cells
   (a) Types (neutrophil cells and mononuclear cells)
   (b) Sites (perivascular or vascular wall)

C. Quantification

Identify arteries by type of accompanying airways. An assessment of the number of affected vessels in proportion to total vessels at a given airway level should be given. The number of vessels in relation to the alveoli should be determined.

II. Lung Tissue

A. Components

Pre- and intra-acinar airway, alveoli, interstitium, and pleura

The description should include:

- Source of tissue –
  (post-mortem, explant, or open lung biopsy) with a comment on size
- Sample site –
  lobe, central or peripheral (avoid the lingula)
- Preparation of tissue –
  (fixation in inflation either via airways or by needle injection of unclamped biopsy are preferred)
- Stains –
  H and E, pentachrome, α-actin, factor VIII and iron.

COMMENTS

- Description of state of inflation and adequacy of sample size, airway and parenchyma including evidence of associated parenchymal disease
- Any other abnormalities or hemorrhage

Interpretation of the pathologic findings should be made in relation to the biochemical, radiologic, clinical and hemodynamic findings, to help guide the clinician. Are the pathologic findings consistent with the clinical picture? A diagnosis should be made where possible.

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PATHOBIOLOGY OF PULMONARY HYPERTENSION

OVERVIEW

The aim of research in pathobiology is to discover the molecular process(es) behind the complex vascular changes associated with pulmonary hypertension.

Progress already realized from research in pathobiological mechanisms include:

- A description of phenotypic changes in endothelial and smooth muscle cells in hypertensive pulmonary arteries
- Recognition that cell proliferation contributes to the structural changes associated with the initiation and progression of pulmonary hypertension
- Recognition that apoptosis contributes to hypertensive pulmonary vascular disease
- Recognition of the role of matrix proteins and matrix turnover in vascular remodeling
- Recognition of the importance of hemodynamic influences on the disease process
- The development of a rationale for effective treatments directed towards specific pathobiologic processes

It is clear that gene expression in pulmonary vascular cells responds to environmental factors, growth factors, receptors, signaling pathways and genetic influences, which interact with each other. Examples of effector systems controlled by gene expression include:

- Transmembrane transporters
- Ion channels
- Transcription factors
- Modulators of apoptosis
- Kinases
- Cell to cell interactive factors (e.g., integrins and membrane receptors)
- Mechano-transducers
- Extracellular matrix turnover
- Growth factors/cytokines and chemokine networks

RECENT FINDINGS

The levels of investigation in the pathobiology of pulmonary hypertension include biochemical, cellular, integrated system and experimental models, and measurements in humans. Potentially important pathophysiologic processes which have been identified from descriptive studies from patients are listed

below. In most cases, it remains unclear whether the observations made are a cause or consequence of the disease.

Potassium Channels

Inhibition of the voltage regulated (Kv) potassium channel by hypoxia or drugs can produce vasoconstriction and has been described in pulmonary artery smooth muscle cells harvested from patients with PPH. It is therefore possible that defects in the potassium channel of pulmonary resistance smooth muscle cells are involved in the initiation and/or progression of pulmonary hypertension. It is possible that a genetic defect related to potassium channels in the lung vessels of PPH patients leading to vasoconstriction is central to the development of PPH is some patients.

Vasoconstrictor/Vasodilator Imbalance

An imbalance may exist in the vasoconstricting and vasodilating mediators or substances involved in control of pulmonary vascular tone. These include the prostacyclin versus thromboxane ratio, an increase in endothelin, a decrease in nitric oxide production or release of other vasoactive substances yet to be described. In addition, other factors might be involved such as serotonin, platelet derived growth factor, angiotensin, or the loss of pulmonary vascular prostacyclin synthase gene expression. Vasoconstrictors may also serve as factors or co-factors which stimulate smooth muscle growth or matrix elaboration.

Prostacyclin Synthase Expression

The loss of the expression of the prostacyclin synthase enzyme and gene in lungs of patients with severe pulmonary hypertension is consistent with a decrease in pulmonary prostacyclin production. The loss of prostacyclin synthase expression is likely one manifestation of an altered pulmonary hypertensive endothelial cell phenotype.

Nitric Oxide Production and Chemistry

Reduced expression of nitric oxide synthase in the endothelium of patients with pulmonary hypertension has been demonstrated and correlates inversely with the extent and severity of morphologic lesions. Although it is unsettled as to whether or not this a cause or result of the disease, it is consistent with endothelial dysfunction underlying PPH as part of the disease process. Nitric oxide is important in the signal transduction of angiogenesis, as VEGF receptor activation results in increased nitric oxide production. Similarly, the expression of endothelin 1 is inversely related to that of nitric oxide synthase. These findings suggest that whether or not abnormal endothelial function is the underlying cause of PPH, the progression of the disease is invariably accompanied by a worsening of endothelial function that itself can promote disease progression.

Inflammation

Mediators of inflammation can cause vasoconstriction and cell growth in animal models where inflammation is associated with pulmonary hypertension. The presence of mast cells in the pulmonary vasculature of patients with PPH, and increased levels of TGF-β, interleukin 1 and 6, and the chemokine MIP 1α has been described in patients with PPH. 5-lipoxygenase (5-LO), and 5-lipoxygenase activating protein (FLAP) over-expression have also been described in PPH.

SEROTONIN

Serotonin is a pulmonary vasoconstrictor and growth factor for vascular smooth muscle cells. It has not been established whether serotonin is essential to PPH, but elevations of plasma serotonin levels and impaired platelet storage of serotonin in patients with PPH have been described, and these have persisted in patients with PPH following lung transplantation.

ANGIOGENESIS

Misguided angiogenesis has been suggested as one mechanism for the development of plexiform lesions. One study has suggested that monoclonal expansion of endothelial cells occurs in PPH and is the basis for the plexiform lesion, whereas plexiform lesions in secondary pulmonary hypertension are polyclonal, suggesting that they occur via pathogenetically different routes. It is possible that medial hypertrophy and hyperplasia are early changes that result from misguided angiogenesis, as a consequence of a phenotypically altered endothelial cell.

THROMBOSIS

Thrombosis in situ of the pulmonary vascular bed has been proposed as a causative or contributing feature of pulmonary hypertension. Abnormalities in platelet activation and function, and biochemical features of a procoagulant environment within the pulmonary vasculature support a potential role of thrombosis in disease initiation in some patients. The interaction between growth factors, platelets, and the vessel wall suggest that thrombosis may play a fundamental role between many of the described pathobiologic processes in PPH and disease progression.

HEMODYNAMICS AND SHEAR STRESS

Several studies suggest that local hemodynamics can influence pulmonary vascular remodeling. A classic example is the pulmonary hypertension that occurs in congenital systemic to pulmonary shunts. It is believed that endothelial cells release mediators that induce vascular smooth muscle cell growth. Experimental data suggests that medial hypertrophy can be converted into a neointimal pattern when pulmonary vascular injury is coupled with increased blood flow. These neointimal lesions are composed of smooth muscle cells since they are immunoreactive to anti-α smooth muscle actin antibody. It is now accepted that hemodynamic shear stress acts through the endothelium to regulate vessel tone and in the chronic restructuring of blood vessels. Thus, the endothelium serves as a complex mechanical signal transduction interface between blood flow and the vessel wall.

EXTRACELLULAR MATRIX

Several studies demonstrate persistent matrix protein synthesis in pulmonary arteries obtained from patients with severe PPH. The observation that these pulmonary arteries are actively remodeling provides the rationale for developing pharmacologic inhibitors of remodeling that may halt, or even reverse, progression of disease.

FUTURE GOALS OF PATHOBIOLOGIC RESEARCH

- To discover the final common pathways for pulmonary hypertensive diseases
- To identify candidate genes for sporadic and familial PPH
- To identify the causative molecular process that are linked to epidemiologic risk factors
- To develop molecular biochemical and physiologic tests to monitor and diagnose the disease
- To develop new treatments based on established pathobiologic mechanisms

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RISK FACTORS AND ASSOCIATED CONDITIONS FOR PULMONARY HYPERTENSION

A risk factor for pulmonary hypertension is any factor or condition that is suspected to play a causal or facilitating role in the development of the disease. Because risk factors relate to the probability of occurrence of the disease, they must be present prior to the onset of the disease. Risk factors may include drugs, chemical products, diseases or a clinical state (age, gender). When it is not possible to determine whether a factor was present before the onset of the PPH, and thus it is unclear whether it played a causal role, the term "associated condition" is used. Associated conditions can be diseases that occur together with primary pulmonary hypertension, and thus are the result of a common risk factor. When associated conditions appear after the onset of PPH, it may be possible that PPH is a risk factor for that condition.

Conclusions regarding the causal relationship between risk factors and the development of PPH relate to the magnitude of the association, the temporality of the association, and consistency of the observations. The clinical features of PPH in patients with known risk factors are generally determined by the severity of the

PPH, and whatever influences the risk factor has on the overall medical condition. For example, the association of PPH and cirrhosis would have the combined clinical features of PPH and liver disease.

The exact mechanism by which the risk factors produce PPH has not been established. Given the fact that the absolute risk is generally low, factors of individual susceptibility are likely to play an important role.

The following risk factors have been categorized based on the strength of the association with PPH and their probable causal role. "Definite" indicates an association based on several concordant observations, including a major controlled study or a clear epidemic. Definite risk factors are considered to play a causal role in the development of the disease. "Very likely" indicates several concordant observations (including large case series and studies) that are not attributable to considered biases, or a general consensus among experts. "Possible" indicates as association based on case series, registries, or expert opinions. "Unlikely" indicates risk factors that have been proposed but have not been found to have any association from controlled studies.

A. Drugs and Toxins

1. Definite

- Aminorex
- Fenfluramine
- Dexfenfluramine
- Toxic Rapeseed Oil

2. Very Likely

- Amphetamines
- L-tryptophan

3. Possible

- Meta-amphetamines
- Cocaine
- Chemotherapeutic Agents

4. Unlikely

- Antidepressants
- Oral Contraceptives
- Estrogen Therapy
- Cigarette Smoking

B. Demographic and Medical Conditions

1. Definite

- Gender

2. **Possible**
   - Pregnancy
   - Systemic Hypertension
3. **Unlikely**
   - Obesity

C. **Diseases**

1. **Definite**
   - HIV Infection
2. **Very likely**
   - Portal Hypertension / Liver Disease
   - Collagen Vascular Diseases
   - Congenital Systemic-Pulmonary Cardiac Shunts
3. **Possible**
   - Thyroid disorders

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GENETICS OF PULMONARY HYPERTENSION

FAMILIAL PPH

PPH has been diagnosed in families worldwide. Currently there are 72 known families in the U.S., 10 in Australia, 8 in England, 3 in Canada and 1 in Germany. The prevalence of genetic or familial PPH is uncertain but is at least 6% of all PPH cases and may be considerably higher.

The transmission and development of PPH in families has many unique features. The age of onset is variable and the penetrance is incomplete. Many individuals in families with PPH inherit the gene and have progeny with PPH yet never develop PPH. The observation that there are fewer males born in PPH

families than in the population at large suggests that the PPH gene might influence fertilization or cause male fetal wastage.

Patients with familial PPH have a similar female to male gender ratio, age of onset and natural history of the disease as those with "sporadic" PPH. The documentation of familial PPH can be difficult since remote common ancestry occurs in patients with apparently sporadic PPH, and skipped generations due either to incomplete penetrance or variable expression can mimic sporadic disease. Because the clinical and pathologic features of familial and sporadic PPH are virtually identical, it seems likely that the same gene(s) may be involved in both forms of the disease. It also seems likely that the disease will not be due to an abnormal gene product resulting from a mutation, but will be due to abnormal production or regulation of a normal gene product.

Vertical transmission has been demonstrated in as many as five generations in one family and is highly indicative of a single dominant gene which is believed to be autosomal for PPH. Genetic anticipation has been evident in familial PPH since early reports. Trinucleotide repeat expansion, originally described in several neurologic disorders, remains the only known biologic explanation for genetic anticipation in PPH and raises the possibility that the pathogenesis of familial PPH might have a neurologic basis. The entire spectrum of pathologic features associated with sporadic PPH, including plexogenic arteriopathy, thromboembolic arteriopathy, veno-occlusive disease and pulmonary capillary hemangiomatosis have been reported in different families with PPH.

The locus of a gene linked to familial PPH has been identified on chromosome 2q31-32, and analysis of the genome containing the gene has been reduced to less than 7 million base pairs. Investigators have reported positive results of microsatellite marker investigations which link familial PPH to the same 25-27 region on chromosome 2q31-32. PPH 1 is the Human Genome Organization approved designation DGB:1381541. The clinical transmission of the gene is typical of other genetic diseases that are based on expanded trinucleotide repeats, but may involve abnormal promoter or modifier gene functions as well. The low penetrance of this gene confers only about a 10-20% likelihood of developing the disease.

COUNSELING PATIENTS WITH FAMILIAL PPH

A complete family history should be obtained on every patient with PPH in order to explore the possibility of familial disease. Because lifetime penetrance is only 10-20% even if the gene is present, the likelihood of a first degree relative being affected when only one person in a family has PPH is estimated at .6-1.2%. If there is a second case known in the family, the risk rises to 5-10% lifetime. Based on current data, it is unlikely that screening the family members for the presence of disease will be of value when one member of the family has PPH. Children of an affected parent, with familial PPH, have only a 5-10% lifetime risk of developing the disease. Although clinical screening of asymptomatic family members will have a low yield, individual clinicians and families may opt to do so because of the severity of the disease.

Most experts currently advise against recommending genetic testing of family members in families with familial PPH because knowledge of the gene and its relationship to the disease is not advanced enough to provide true informed consent to anyone requesting the test. However, in large families where a sufficient

number of DNA samples can be collected, it is possible to provide information on carrier status by constructing genetic haplotypes.

IMMUNOGENETICS

Although PPH has been associated with autoimmune phenomena, the association remains unclear. The data suggest that a subset of patients with PPH may have a genetically programmed and immunologically mediated component to their pulmonary hypertension which may predispose them to developing a diagnosable connective tissue disease over time.

FUTURE RESEARCH

At the present time efforts are being focused towards the actual identity of the PPH 1 gene. This will allow studies of gene regulation and function, the use of transgenic and knockout animal models, as well as transfection with native missense plasmids to clarify the pulmonary vascular and embryological and systemic effects of the gene and its product. It is conceivable that the gene may be highly polymorphic. If it contains an unstable trinucleotide repeat expansion, then the number of repeats will likely determine the penetrance and probably the severity of the disease.

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DIAGNOSIS AND ASSESSMENT OF PULMONARY HYPERTENSION

The diagnostic strategy for evaluating patients with pulmonary hypertension is well accepted with a high degree of consensus among experienced clinicians. Utilizing current medical technology, the correct diagnosis and assessment of the severity of pulmonary hypertension in a given individual can be made with a high level of confidence. The consensus regarding the general diagnostic approach to pulmonary hypertension now permits focusing on specific problematic areas.

SCREENING FOR PULMONARY HYPERTENSION

Screening appropriate patient populations may lead to the early identification of pulmonary hypertension in asymptomatic or minimally symptomatic individuals, or in symptomatic patients in whom the diagnosis was not previously suspected. This could allow early initiation of treatments at a time when dynamic or reversible pathogenic mechanisms are present, increasing the likelihood of a successful treatment outcome. Screening tests should be noninvasive and low risk, if possible, and have a relatively high sensitivity and specificity for detecting pulmonary hypertension.

Screening may be appropriate in groups of patients at increased risk of developing pulmonary hypertension. In such instances, general screening should always begin with a thorough clinical interview to elicit symptoms consistent with pulmonary hypertension, and a thorough physical examination to elicit physical findings consistent with the diagnosis. When the history and physical examination are inconclusive, further diagnostic testing may be appropriate.

The following recommendations are made regarding specific subgroups of patients. A transthoracic echocardiogram is currently the preferred screening test for the presence of pulmonary hypertension.

CONNECTIVE TISSUE DISEASES

The Scleroderma Spectrum of Diseases

Because of the high prevalence of pulmonary hypertension in these patients, as well as the availability of effective treatments, a transthoracic echocardiogram is recommended to be performed annually in patients with or without symptoms of pulmonary hypertension.

Systemic Lupus, Rheumatoid Arthritis, and Other Connective Tissue Diseases

Because of the low prevalence of pulmonary hypertension, and the lack of established effective treatment, a transthoracic echocardiogram is recommended only if patients have symptoms suggestive of pulmonary hypertension.

FAMILIES OF DOCUMENTED PPH

A detailed family history should be taken at the time the diagnosis of PPH is made in the proband. It is reasonable to consider a transthoracic echocardiogram in the first degree relatives at the time of diagnosis, at any time symptoms consistent with pulmonary hypertension arise, or every three to five years in asymptomatic individuals. In addition, relatives should be made aware of symptoms consistent with pulmonary hypertension. The basis for these recommendations is the greater prevalence of familial PPH than previously reported, and the availability of effective treatments. In addition, screening asymptomatic family members will help gather additional information about the prevalence of familial PPH and the effectiveness of early intervention.

LIVER DISEASE/PORTAL HYPERTENSION

Because pulmonary hypertension in these patients renders them at very high risk for liver transplantation, and because there is effective treatment available, a transthoracic echocardiogram should be performed in all patients when they are evaluated for liver transplantation.

HIV Infection

Because of the low prevalence of pulmonary hypertension in this subgroup, a transthoracic echocardiogram is recommended only in subjects who are HIV positive if they have symptoms consistent with pulmonary hypertension.

Patients with a History of Intravenous Drug Use

Because the prevalence of pulmonary hypertension is uncertain in this subgroup, a transthoracic echocardiogram is recommended only in those patients who have symptoms consistent with pulmonary hypertension.

Patients with a History of Appetite-Suppressant Drug Use

Because of the low prevalence of pulmonary hypertension in this subgroup, a transthoracic echocardiogram is recommended only in patients who have symptoms consistent with pulmonary hypertension.

THE EVALUATION OF MILD PULMONARY HYPERTENSION

The widespread use of Doppler echocardiography in the assessment of nonspecific cardiovascular symptoms or signs has led to occasional observations of mildly increased right ventricular systolic pressure. Mild pulmonary hypertension is defined as a systolic pulmonary artery pressure of 40-50 mmHg, which corresponds to a tricuspid regurgitant velocity on Doppler echocardiography of 3.0-3.5 m/sec. The following recommendations are made regarding the assessment of mild pulmonary hypertension.

Asymptomatic Individuals (Incidental Discovery)

It is recommended that a Doppler echocardiogram be repeated in six months along with a detailed history and physical examination.

Symptomatic Individuals

It is recommended that signs of pulmonary hypertension warrant right heart catheterization for confirmation of the hemodynamic findings. If the right heart catheterization does not reveal pulmonary hypertension at rest, it is recommended that pulmonary hemodynamics be measured during exercise. Patients in whom mild pulmonary hypertension exists at rest, or develops with exercise, should be managed like other patients with pulmonary hypertension.

High Risk Individuals

Individuals who are asymptomatic but at high risk of developing pulmonary hypertension should have a Doppler echocardiographic exam repeated in six months. If the presence of mild pulmonary hypertension is confirmed, they should undergo the same evaluation as do patients with symptomatic pulmonary hypertension.

MEDICAL TESTING TO CHARACTERIZE PULMONARY HYPERTENSION

Recent advances in medical technology have greatly improved noninvasive measurements rendering them more precise, reproducible, and reflective of the underlying pathophysiology of the disease.

ECHOCARDIOGRAPHY WITH DOPPLER

The following parameters are suggested for measurement:

- tricuspid regurgitant velocity
- pulmonary artery systolic flow acceleration time
- right ventricular ejection time
- right ventricular dimensions
- right ventricular volumetric data
- right ventricular index of myocardial performance
- timing of mid-systolic deceleration of right ventricular ejection

Echocardiography with Doppler may be useful in the follow-up of patients with pulmonary hypertension to monitor progression of the disease and/or the response to therapy.

MAGNETIC RESONANCE IMAGING (MRI)

The following parameters may be useful in evaluating the patient:

- right ventricular morphology
- right atrial morphology
- pulmonary artery morphology
- right ventricular function

The value of serial MRI scans in following the course of patients is not established.

COMPUTED TOMOGRAPHY (CT) OF THE CHEST

The following parameters may be useful in evaluating the patient:

- right ventricular morphology
- right atrial morphology
- pulmonary artery morphology
- right ventricular function.

It is recommended that a high-resolution chest CT scan also be performed to evaluate the lung parenchyma and to detect the presence of pulmonary venocclusive disease.

The value of serial chest CT scans in following the course of patients is not established.

Exercise Testing

A six-minute walk test or a cardiopulmonary exercise test is recommended in patients at the time of diagnosis and follow-up. Exercise tests best characterize the functional impairment of patients with PPH, and their response to therapy.

Right Heart Catheterization

Right heart catheterization is recommended for all patients who are undergoing an evaluation of pulmonary hypertension. Measurements during catheterization should include the following:

- right atrial pressure
- right ventricular systolic and end-diastolic pressure
- pulmonary artery systolic, diastolic, and mean pressure
- pulmonary capillary wedge pressure
- systemic and pulmonary arterial oxygen saturation
- cardiac output

Vasodilator Testing

It is recommended that all patients undergo acute testing with a short-acting vasodilator to determine vasodilator responsiveness at the time of their initial right heart catheterization. The following vasodilators are recommended:

- intravenous epoprostenol sodium
- inhaled nitric oxide
- intravenous adenosine

Patients who appear responsive to acute vasodilator testing may have a favorable response to treatment with oral calcium channel blockers. Although there is no consensus about the definition of vasodilator responsiveness, a minimum acceptable response would be a reduction in mean pulmonary artery pressure of 10 mm/Hg associated with either no change or an increase in cardiac output. Patients who do not manifest responsiveness to acute vasodilator challenge are unlikely to have clinical benefit from oral calcium channel blocker therapy.

Assessment of Pulmonary Arterial Impedence

Measurements of the impedence of the pulmonary vascular bed, using the acceleration time interval measurements (AcT), may provide additional information about right ventricular performance. Impedence parameters may better reflect true right ventricular afterload and provide hemodynamic information beyond that derived from measurements of pressure and flow. Accurate assessment of impedence can be done at the time of cardiac catheterization using high-fidelity multisensor pressure and velocity transducers.

Lung Biopsy

Although pathologic assessment of the lung may provide insights into histopathologic characteristics of pulmonary hypertensive states, the procedure entails a risk and there is little evidence that it provides additional clinically useful information over careful noninvasive and hemodynamic assessment in most

patients. Lung biopsy cannot be recommended as a part of the routine evaluation of patients with suspected PPH. It should be considered when there appears to be a specific indication, such as a diagnosis of active vasculitis.

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MEDICAL THERAPY OF PULMONARY HYPERTENSION

Over the past 25 years there has been considerable experience with a variety of medications for the treatment of primary pulmonary hypertension. The clinical experience with these medications are summarized.

CALCIUM CHANNEL BLOCKERS

RATIONALE

Calcium channel blockers are a chemically heterogeneous group of compounds that inhibit calcium influx through the slow channel into cardiac and smooth muscle cells. Their usefulness in PPH is believed to be based on the ability to cause vasodilatation of pulmonary vascular smooth muscle. They also produce electrophysiologic effects, possess negative inotropic properties and cause reflex increases in beta adrenergic tone.

EFFECTIVENESS

The data demonstrates that a minority (approximately 20%) of patients with PPH will respond to oral calcium channel blockers, documented by an improvement in symptoms and exercise tolerance, hemodynamics via a reduction in pulmonary artery pressure and an increase in cardiac output, and survival. Although most studies have used calcium channel blockers at relatively high doses, the optimal dosing of patients with PPH is uncertain. The direct effect of calcium channel blockers on pulmonary vessel wall biology is unknown.

Patients with no evidence of an acute hemodynamic response to these drugs are unlikely to benefit from chronic therapy. Because of the frequent reporting of significant adverse effects of calcium blocker in these patients, which include systemic hypotension, pulmonary edema, right ventricular failure, and death, it is not recommended that calcium channel blockers be used in patients in whom acute effectiveness has not been demonstrated.

FUTURE DIRECTIONS

Enhanced effects of calcium channel blockers when used in conjunction with intravenous vasodilators and oral thromboxane synthase inhibitors has been reported. It is recommended that the use of calcium channel blockers in combination with other treatments be pursued.

INOTROPIC AGENTS

RATIONALE

As the cause of death in patients with PPH is primarily right heart failure, the use of drugs that will improve right ventricular performance is warranted. Currently there are no data on the use of chronic inotropic therapy as a treatment of PPH. The experience of an increased mortality in patients with left heart failure treated with a chronic inotropic therapy is of concern.

EFFECTIVENESS

Class I Agents

These agents augment contractility by increasing intracellular cAMP and calcium. The short term use of parenteral inotropes may be of benefit in some circumstances.

Class II Agents

Digoxin has been shown to increase cardiac output and reduce circulating norepinephrine acutely in patients with PPH. Digoxin has also been shown to be chronically effective in patients with left ventricular failure. Digoxin is used by some experts in the management of PPH for these reasons.

FUTURE DIRECTIONS

A better understanding of the neurohumoral and hemodynamic effects of inotropic therapy in patients with PPH is necessary. Strategies should also be developed to attempt to restore normal gene expression of sarcomere proteins to improve the contractile performance of the cardiac myocytes.

ANTICOAGULANTS

RATIONALE

Histologic data demonstrating thrombotic lesions in small pulmonary arteries in a large percent of patients with PPH and biochemical data consistent with a hypercoaguable state in some patients with PPH provide a rationale for the use of anticoagulants in PPH.

EFFECTIVENESS

Clinical data supporting the chronic use of anticoagulation is limited but supportive. Warfarin has been shown to be associated with improved survival in one retrospective study of PPH, one retrospective study of patients with PPH associated with the use of aminorex, and one prospective study of PPH. The optimal dose of warfarin in these studies was not determined. The range of anticoagulation that is recommended is an INR of 1.5 to 2; however, different clinical circumstances may require adjustment of the range.

FUTURE DIRECTIONS

New antithrombotic and anticoagulant drugs are being evaluated for several different clinical entities. Drugs that might be of promise in patients with PPH include monoclonal antibodies and other agents that block the glycoprotein IIb/IIIa platelet receptor, thromboxane synthase inhibitors and receptor blockers, and heparins and heparin-like compounds.

PROSTAGLANDINS

RATIONALE

The use of prostacyclin or an analogue as a treatment of PPH is supported by the demonstration of an imbalance of thromboxane to prostacyclin metabolites in patients with PPH, and the demonstration of a reduction in prostacyclin synthase in the pulmonary arteries of patients with PPH.

EFFECTIVENESS

Continuous intravenous prostacyclin has been evaluated in prospective, randomized clinical trials of PPH. The results confirm an improvement in exercise tolerance, hemodynamics, and survival in patients who are Functional Class III and Class IV. The mechanism of action of the chronic effects of prostacyclin is unknown in these patients, but it is likely multifactorial. Clinical data suggests that it lowers the pulmonary artery pressure, raises the cardiac output, improves systemic oxygen transport, and possibly reverses pulmonary vascular remodeling. Studies have also demonstrated that the lack of an acute response to prostacyclin does not preclude a chronic beneficial response. The development of tolerance to the effects of intravenous prostacyclin is common, and appears to respond to periodic dose escalation. However, the optimal dosing of intravenous prostacyclin for PPH remains uncertain.

FUTURE DIRECTIONS

Studies are necessary to clarify the mechanisms of action of prostacyclin on cardiac and vascular tissue. A better understanding of how to determine the optimum dosing of patients on intravenous prostacyclin is essential. Alternate delivery systems may enhance efficacy, improve safety, and reduce side effects. Trials looking at the effectiveness of prostacyclin analogues administered subcutaneously, by inhalation, and orally, are warranted. The use of these agents in less severely ill patients will be desirable as less complex delivery systems become available. Drugs that increase endogenous prostacyclin production should be pursued.

NITRIC OXIDE

RATIONALE

Nitric oxide activates guanylate cyclase in pulmonary vascular smooth muscle cells which increases cGMP and decreases intracellular calcium concentration, thereby leading to smooth muscle relaxation. When inhaled, the rapid combination of nitric oxide with hemoglobin inactivates any nitric oxide diffusing into the blood, preventing systemic vasodilatation. Consequently nitric oxide is a potent and selective pulmonary vasodilator when administered by inhalation.

EFFECTIVENESS

Although there is a considerable experience in the use of nitric oxide as a short-term treatment of pulmonary hypertension in a variety of clinical situations, the role of nitric oxide as a chronic therapy for PPH remains investigational. The mechanism of beneficial effects of nitric oxide in PPH, both acutely and chronically are likely multifactorial.

FUTURE DIRECTIONS

More data is needed regarding the long-term efficacy and safety of chronic nitric oxide as inhalation therapy. Preliminary studies suggest the pursuit of nitric oxide potentiating compounds, such as phosphodiesterase inhibitors, is warranted. Histologic studies demonstrating reduced levels of nitric oxide synthase in the pulmonary vasculature of patients with PPH provides justification for the development of gene replacement therapy for this disease.

FUTURE DIRECTIONS FOR MEDICAL THERAPY

Considerable promise exists in the development of medical therapy for PPH following a wide variety of approaches. These include:

- studies of myocardial protein and genotypes
- development of vascular antiproliferative agents (including angiotensin converting enzyme inhibitors and endothelin receptor blockers)
- development of agents that affect ion channel function (such as potassium channel openers)
- studies of endothelial derived substance synthesis and metabolism
- studies of genotype and gene expression
- studies evaluating multimodal/combination therapies

Studies of the pathobiology of PPH have demonstrated abnormalities in cellular function of different cell types and sequential changes in vascular morphology and function leading to remodeling. These observations provide targets for the use of several agents in combination, and/or the staging of therapies. In addition to the reversal of remodeling, stimulation or enhancement of normal endothelial cell function may be possible.

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ATRIAL SEPTOSTOMY FOR PULMONARY HYPERTENSION

RATIONALE

The rationale for the creation of an atrial septostomy in PPH is based on experimental and clinical observations suggesting that an intra-atrial defect allowing right to left shunting in the setting of severe pulmonary hypertension might be of benefit. Although there exists a worldwide experience in over 60 patients, the procedure should still be considered investigational. Nonetheless, atrial septostomy may represent a real alternative for selected patients with severe PPH. Indications for the procedure include:

- recurrent syncope and/or right ventricular failure despite maximum medical therapy
- as a bridge to transplantation if deterioration occurs despite maximum medical therapy
- when no other option exists

As the disease process in PPH appears to be unaffected by the procedure, the long-term effects of an atrial septostomy must be considered to be palliative.

GUIDELINES

The procedure-related mortality with atrial septostomy in patients with PPH is high, and thus the following recommendations are made to minimize the risk:

- atrial septostomy should only be attempted in institutions with an established track record in the treatment of advanced pulmonary hypertension and an experience in performing atrial septostomy with low morbidity
- atrial septostomy should not be performed in the patient with impending death and severe right ventricular failure, on maximal cardiorespiratory support.

Predictors of procedure-related failure or death include:

- a mean right atrial pressure > 20 mmHg
- a PVR index > 55 U·M^2
- a predicted one year survival less than 40%

Candidates for atrial septostomy should have a systemic arterial oxygen saturation on room air of greater than 90%. During the atrial septostomy procedure it is recommended that the patient have the following:

- mild and appropriate sedation to prevent anxiety
- supplemental oxygen
- careful monitoring of hemodynamics with particular monitoring of the systemic arterial oxygen saturation

The endpoint for the procedure should be considered a reduction in systemic arterial oxygen saturation of 5-10%. It is also recommended that the procedure be performed in a stepwise manner, to create the smallest possible septal defect that will produce hemodynamic changes

Before and after septostomy, transfusion of packed red blood cells or the use of erythropoietin may be necessary to increase oxygen delivery. Chronic anticoagulation is also recommended.

FUTURE RESEARCH

- The optimal timing of the intervention remains uncertain. Investigations should address whether or not the intervention should be performed earlier in the course of the disease.
- The mechanisms responsible for beneficial effects of atrial septostomy remain unclear. Possibilities that exist include:
  - Increased oxygen delivery at rest and/or with exercise
  - Reduced right ventricular end diastolic pressure or wall stress
  - Improvement of right ventricular dysfunction by Frank Starling mechanism or relief of ischemia
- Long-term effectiveness and possible undesirable effects need to be studied.

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TRANSPLANTATION FOR PULMONARY HYPERTENSION

RATIONALE

Transplantation is an effective treatment for patients with advanced pulmonary hypertension. Since 1981, close to 1000 patients have undergone either a single lung, double lung or heart-lung transplant for pulmonary hypertension worldwide. Ages of recipients range from 2 months to 61 years. The operative mortality ranges between 16-29% and is affected by the primary diagnosis. PPH recipients of a single lung transplant appear to have a higher operative mortality than those undergoing transplantation for other conditions, whereas recipients of double lung or heart-lung transplant appear to have comparable results. The one year survival is between 70-75%, the three year survival between 55-60% and five year survival between 40-45%. The longest survival to date in a heart-lung transplant recipient has been more than 14 years.

GUIDELINES

Transplantation should be reserved for patients with pulmonary hypertension who have progressed in spite of optimal medical management. Advances in the medical therapy of PPH has improved the prognosis for many patients. As progress is made in the medical management of patients with PPH, the indications for transplant may evolve.

Patients should be referred for evaluation for transplantation at the appropriate time. The course of the disease and the waiting time must be taken into account. Timing the referral for transplantation depends on the patient's prognosis with optimal medical management, the anticipated waiting time before transplantation in the region, and the expected survival after transplantation. Guidelines for timing the referral include:

- NYHA Functional Class III or IV in spite of medical therapy
- When treatment with prostacyclin is initiated, or is failing, or is causing intolerable side effects

There are several transplantation options. Acceptable results have been achieved with heart-lung transplantation, bilateral lung transplantation, and single lung transplantation. While there are advantages and disadvantages to each operation, there is currently no consensus regarding the best procedure. The availability of donor organs often influences the choice of procedure. It is possible that data on long-term survival in transplant recipients may demonstrate a survival advantage of one procedure over another.

While traditional measures such as survival and cardiopulmonary function have been emphasized, quality of life is equally important. Several studies have documented a significant improvement in both overall and health-related quality of life after heart/lung and lung transplantation for pulmonary hypertension. Only pilot studies have addressed the issue of cost effectiveness. When considering the cost effectiveness of transplantation, one needs to account for the anticipated medical care of the advanced PPH patient who often requires frequent hospitalization, and the expense of newer therapies, such as intravenous prostacyclin therapy at the present time.

FUTURE DIRECTIONS

Living related donor transplantation is controversial. Although related living donor lung transplantation has been successful, there is very limited experience in children and no known experience in adults with pulmonary hypertension. Extreme caution is advised when considering this approach at this time.

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NOMENCLATURE AND CLASSIFICATION OF PULMONARY HYPERTENSION

A diagnostic classification of the various forms of pulmonary hypertension can be helpful in communicating about individual patients and in standardizing diagnosis and treatment. Pulmonary hypertension can be classified in many ways. Several previous classifications have proved to be problematic.

The following is proposed to allow the categorization by common clinical features. This classification reflects recent advances in the understanding of pulmonary hypertensive diseases, and recognizes the similarity between primary pulmonary hypertension and pulmonary hypertension of certain known etiologies.

(In keeping with the new diagnostic classification, a new pathologic classification of pulmonary hypertension is proposed. The new recommendations for the pathologic characterization of pulmonary hypertensive states are included in the Pathology section.)

DIAGNOSTIC CLASSIFICATION

1. Pulmonary Arterial Hypertension
   - 1.1 Primary Pulmonary Hypertension
     - (a) Sporadic
     - (b) Familial
   - 1.2 Related to:
     - (a) Collagen Vascular Disease
     - (b) Congenital Systemic to Pulmonary Shunts
     - (c) Portal Hypertension

(d) HIV Infection

(e) Drugs / Toxins

(1) Anorexigens

(2) Other

(f) Persistent Pulmonary Hypertension of the Newborn

(g) Other

2. Pulmonary Venous Hypertension

2.1 Left-Sided Atrial or Ventricular Heart Disease

2.2 Left-Sided Valvular Heart Disease

2.3 Extrinsic Compression of Central Pulmonary Veins

(a) Fibrosing Mediastinitis

(b) Adenopathy / Tumors

2.4 Pulmonary Veno-Occlusive Disease

2.5 Other

Pulmonary Hypertension Associated with Disorders of the Respiratory System and/or Hypoxemia

3.1 Chronic Obstructive Pulmonary Disease

3.2 Interstitial Lung Disease

3.3 Sleep Disordered Breathing

3.4 Alveolar Hypoventilation Disorders

3.5 Chronic Exposure to High Altitude

3.6 Neonatal Lung Disease

3.7 Alveolar-Capillary Dysplasia

3.8 Other

4. Pulmonary Hypertension due to Chronic Thrombotic and/or Embolic Disease

4.1 Thromboembolic Obstruction of Proximal Pulmonary Arteries

4.2 Obstruction of Distal Pulmonary Arteries

(a) Pulmonary Embolism (Thrombus, Tumor, OVA and/or parasites, Foreign Material)

(b) In-situ Thrombosis

(c) Sickle Cell Disease

5. Pulmonary Hypertension due to Disorders Directly Affecting the Pulmonary Vasculature

5.1 Inflammatory

(a) Schistosomiasis

(b) Sarcoidosis

(c) Other

5.2 Pulmonary Capillary Hemangiomatosis

FUNCTIONAL ASSESSMENT *

A. Class I – Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

B. Class II – Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

C. Class III – Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or near syncope.

D. Class IV – Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

* modified after the New York Heart Association Functional Classification

Reference

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APPETITE-SUPPRESSANT DRUGS AND THE RISK OF PRIMARY PULMONARY HYPERTENSION

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ABSTRACT

Background Recently in France, primary pulmonary hypertension developed in a cluster of patients exposed to derivatives of fenfluramine in appetite suppressants (anorexic agents), which are used for weight control. We investigated the potential role of anorexic agents and other suspected risk factors for primary pulmonary hypertension.

Methods In a case–control study, we assessed 95 patients with primary pulmonary hypertension from 35 centers in France, Belgium, the United Kingdom, and the Netherlands and 355 controls recruited from general practices and matched to the patients' sex and age.

Results The use of anorexic drugs (mainly derivatives of fenfluramine) was associated with an increased risk of primary pulmonary hypertension (odds ratio with any anorexic-drug use, 6.3; 95 percent confidence interval, 3.0 to 13.2). For the use of anorexic agents in the preceding year, the odds ratio was 10.1 (95 percent confidence interval, 3.4 to 29.9). When anorexic drugs were used for a total of more than three months, the odds ratio was 23.1 (95 percent confidence interval, 6.9 to 77.7). We also confirmed an association with several previously identified risk factors: a family history of pulmonary hypertension, infection with the human immunodeficiency virus, cirrhosis, and use of cocaine or intravenous drugs.

Conclusions The use of anorexic drugs was associated with the development of primary pulmonary hypertension. Active surveillance for this disease should be considered, particularly since the use of anorexic drugs is expected to increase in the near future. (N Engl J Med 1996;335:609-16.)

PRIMARY pulmonary hypertension is a rare, often fatal disease that tends to occur with particular frequency in women during their third or fourth decade.[1,2] The factors leading to its development remain enigmatic. The occurrence of familial primary pulmonary hypertension suggests a genetic susceptibility.[3] Reports have also suggested that portal hypertension[4,5] and recent pregnancy[6] may have causative roles. Exogenous factors have been suspected as well, including cocaine use,[7] infection with the human immunodeficiency virus (HIV),[8] oral-contraceptive use,[9,10] and the use of anorexic agents.[11-13] In the 1960s, there was an epidemic of primary pulmonary hypertension in Switzerland, Germany, and Austria in association with a particular anorexic agent, aminorex fumarate.[11] In the early 1990s, French investigators reported a cluster of cases among patients who had used derivatives of fenfluramine.[13] Dexfenfluramine,

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the main drug thought to be involved, is used to treat obesity.

We sought to assess the incidence of primary pulmonary hypertension and investigate the causative roles of various suspected risk factors, especially anorexic agents.[14]

METHODS

This was a prospective case–control study conducted in four countries (France, Belgium, the United Kingdom, and the Netherlands). The study included men and women 18 to 70 years of age who had lived in the country where they were studied for more than six months, were able to participate in the interview, and did not have another chronic, active, life-threatening disease.

Three hundred six cardiology and pulmonary-medicine centers at large or university-based hospitals, public and private, were contacted in France, Belgium, the United Kingdom, and the Netherlands, and 220 of them agreed to participate. The centers were provided with stamped, preaddressed postcards with which to report cases of primary pulmonary hypertension to local research teams. The centers were also contacted every two to three months by mail or telephone, or they were visited. The medical records of the patients identified were screened at each site by trained specialists who, in almost all instances, were not affiliated with the reporting centers. During the site visits, the diagnostic and reporting process at the centers was reviewed to identify patients with primary pulmonary hypertension who might have been overlooked and assess potential biases in reporting. In Belgium, regular contact was established with each of 71 centers where primary pulmonary hypertension might have been diagnosed. This contact allowed us to calculate the annual incidence of the disease in the Belgian population.

Patients

We recruited patients with primary pulmonary hypertension diagnosed from September 1, 1992, through September 30, 1994, at the time of the patient's first right heart catheterization. The diagnosis required both that pulmonary hypertension be documented and that the following secondary causes be absent: congenital abnormalities of the lungs, thorax, or diaphragm; congenital or acquired valvular or myocardial disease; pulmonary thromboembolism; obstructive lung disease; interstitial lung disease; pulmonary-artery or pulmonary-valve stenosis; pulmonary venous hypertension; central hypoventilation with hypoxemia and hypercapnia; parasitic disease affecting the lungs; sickle cell anemia, the acquired immunodeficiency syndrome (AIDS); and collagen vascular diseases. An international panel of reviewers assessed abstracted medical data, cardiac-catheterization reports, chest radiographs, perfusion lung scans, and echocardiographic images or reports for patients qualifying for the study. The panel, whose members had no knowledge of any patient's exposure to anorexic drugs, classified the patients in three groups: patients with definite primary pulmonary hypertension, those with probable primary pulmonary hypertension, and those who were not considered appropriate for the study. The first two groups were included in the case–control analysis. The reproducibility of the classifications, as verified by a second review of 10 randomly selected files, was excellent (all the decisions to include or exclude patients were confirmed). The results of autopsy or biopsy were obtained for nine patients who underwent transplantation or died soon after their inclusion in the study, and they all had plexogenic pulmonary arteriopathy, regardless of their status with respect to anorexic-drug use.

Controls

Four control patients were sought for each patient with primary pulmonary hypertension. The controls were randomly selected from lists of consecutive patients seen by the same general practitioner as the patient with primary pulmonary hypertension. The general practitioner was identified by the patient and defined as the physician the patient consulted for usual care. If this physician was unavailable (usually because he or she refused to participate in the study), other general practitioners were contacted who practiced in the region where the patient lived. One third of the controls were recruited in this manner. The controls were individually matched to the case patients with respect to age (within five years), sex, and the number of visits to the physician per year (<2 or ≥2). The following data were recorded for all the visits made during a one-week period: the patient's name, age, sex, and the number of visits made by that patient per year. All visits of patients who met the matching criteria were identified, and four controls were randomly selected by the local coordinating center. The general practitioner was contacted again for the names and telephone numbers of the patients selected. The same criteria for inclusion and exclusion were used in selecting the controls that were used in selecting the case patients, except for the diagnosis of primary pulmonary hypertension.

Exposure to Anorexic Drugs

Each patient underwent a thorough, face-to-face interview conducted by a specially trained interviewer who had no medical background and was unaware of the study's main hypotheses. The patients were asked about demographic characteristics; their medical, surgical, and obstetrical histories; and exposure to drugs. Data on such exposures were recorded chronologically on a calendar-like data sheet. The recording of exposures reported to have occurred after August 1, 1989, was more detailed than that of earlier exposures. The presence of HIV infection and the diagnosis of cirrhosis were determined by a review of the medical charts. Drug use was established by three methods: spontaneous reporting by the patient; the presentation to the patient of lists of approximately 80 trade names chosen from among the most commonly prescribed drugs in 17 therapeutic classes (the individual products varied slightly from country to country); and the presentation to the patient of a visual display showing 35 selected packages, tablets, or both. Only exposure to antihypertensive drugs, oral contraceptives, thyroid extracts, and anorexic agents (also called appetite suppressants) was analyzed. The following anorexic agents were considered: derivatives of fenfluramine (fenfluramine and dexfenfluramine), amphetamine-like anorexic agents (diethylpropion [amfepramone], clobenzorex, fenproporex, mazindol, and phenmetrazine), and compound preparations of appetite-suppressant drugs and other drugs taken to lose weight. Special preparations used in order to lose weight, with no reference to appetite suppression, were not considered anorexic agents. Each patient was given a special questionnaire assessing his or her use of illicit drugs (intravenous drugs, cocaine, hashish, and marijuana). The data-collection process was identical in all the countries studied.

For each case patient and that patient's matched controls, the index date used in the study of risk factors corresponded to the date of onset of the case patient's symptoms (usually dyspnea). Patients were classified as having been exposed to a given risk factor if the exposure occurred before the index date (a "definite exposure"). Exposures reported to have occurred at an indeterminate time or during the same month as the index date were classified as "possible exposures." Patients in whom the exposure began after the index date were considered unexposed to that risk factor. Definite exposure to anorexic agents was categorized further, depending on whether the exposure occurred in the 12 months before the index date ("recent use") or had ended more than 12 months earlier ("past use"). Because of the design of the calendar data sheet, this categorization could be used only for 65 case patients and 234 matched controls whose index dates were later than August 1, 1989.

Statistical Analysis

All the odds ratios presented here were obtained through conditional logistic regression. All the models included exposure to

appetite suppressants (categorized as none, possible, or definite, as defined above), weight-related confounding variables, and other variables thought to be possible risk factors. The weight-related variables consisted of the patient's highest lifetime body-mass index (calculated as the weight in kilograms divided by the square of the height in meters and dichotomized as <30 and ≥30, a cut-off point selected a priori), behavior aimed at losing weight (categorized as present or absent, with the former defined as a report of unstable weight; the use of diuretics, laxatives, or phytotherapy for weight loss; or episodes of anorexia); and the use of thyroid extracts (yes or no). The other variables thought to be risk factors were the use of cocaine, intravenous drugs, or both (yes or no); treatment for systemic hypertension (present or absent); and smoking (yes or no). In separate analyses conducted of women, oral-contraceptive use (yes or no) and pregnancy during the year before the index date (yes or no) were also considered, and adjustment was made for them. Variability in sampling associated with the estimated odds ratios was assessed by two-sided 95 percent confidence intervals. All the analyses were performed with the SAS statistical package, version 6.13 (Unix), and Egret, version 026.6. P values of less than 0.05 were considered to indicate statistical significance.

RESULTS

One hundred thirty-five patients with primary pulmonary hypertension met the criteria for inclusion in the study. An additional 26 patients were already dead or were too sick to be interviewed. Twenty-three of the 135 patients were considered by the review panel not likely to have primary pulmonary hypertension, 2 were lost to follow-up, 2 declined to participate, and 13 could not be interviewed, or their data reviewed, before the final analysis. The remaining 95 patients (80 with definite and 15 with probable primary pulmonary hypertension), who were retained in the case-control study, were identified at a total of 35 specialized centers (Table 1). A national referral center for primary pulmonary hypertension in France (Antoine Béclère Hospital)[15] contributed 35 patients; the other centers each contributed 1 to 6 patients (mean, 1.7). The mean (±SD) age of the case patients was 44.7±12.3 years, and that of the controls was 45.1±12.6 years. Among the case patients, the female:male ratio was 2.3:1 (Table 1). Among the controls, the rate of participation was 85.3 percent in France, 92.1 percent in Belgium, 81.8 percent in the United Kingdom, and 100 percent in the Netherlands.

The clinical characteristics of the patients with primary pulmonary hypertension are shown in Table 2. Dyspnea was the initial symptom in 91 percent, and it was severe (New York Heart Association class III or IV) in two thirds at the time of diagnosis. In almost two thirds of these patients, the diagnosis was not established until more than a year had passed after the appearance of symptoms.

The case patients and the controls were very similar with regard to both occupation and 24 broad classes of preexisting morbidity, as defined in the *International Classification of Diseases, Ninth Revision*. The case patients and the controls had taken an almost identical number of drugs (4.4±4.5 and

TABLE 1. CHARACTERISTICS AND COUNTRIES OF THE STUDY POPULATION.

COUNTRY	NO. OF CENTERS	CASE PATIENTS (N=95)	CONTROLS (N=355)
		no. (%)	
France	18		
National referral center		35 (36.8)	117 (33.0)
Other 17 centers		29 (30.5)	115 (32.4)
Belgium	7	13 (13.7)	59 (16.6)
United Kingdom	6	11 (11.6)	36 (10.1)
The Netherlands	4	7 (7.4)	28 (7.9)
All	35		
Women		66 (69.5)	265 (74.6)
Men		29 (30.5)	90 (25.4)
Mean (±SD) age — yr		44.7±12.3	45.1±12.6

TABLE 2. CLINICAL, FUNCTIONAL, AND PULMONARY HEMODYNAMIC VARIABLES IN THE 95 PATIENTS WITH PRIMARY PULMONARY HYPERTENSION.

VARIABLE*	VALUE†
Initial symptoms (% of patients)	
Dyspnea	91
Chest pain	16
Syncope	14
Edema	9
Time from onset of symptoms to cardiac catheterization (% of patients)	
≤12 mo	37
12–35 mo	39
≥36 mo	20
Unknown	4
Severity of dyspnea at diagnosis (% of patients)	
NYHA class I or II	34
NYHA class III or IV	66
Cardiac-catheterization findings (mm Hg)	
Pulmonary arterial pressure	
Systolic	88±21
Diastolic	39±10
Mean	57±13
Pulmonary-capillary wedge pressure	9±3
Right atrial pressure	11±6
Pulmonary-function tests (% of predicted value)	
Forced vital capacity	98±15
Total lung capacity	97±13
FEV_1	91±16
DLCO	79±22
Blood gas measurements	
$PaCO_2$ (mm Hg)	31±5
PaO_2 (mm Hg)	75±20
SaO_2 (%)	94±4

*NYHA denotes New York Heart Association, FEV_1 forced expiratory volume in one second, DLCO single-breath diffusing capacity for carbon monoxide, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, and SaO_2 arterial oxygen saturation.

†Plus–minus values are means ±SD.

4.3±4.4, respectively). Two case patients reported a family history of primary pulmonary hypertension; three had HIV infection (eight with AIDS were excluded from the study at the screening stage); more case patients than controls were alcohol drinkers (72.6 percent vs. 64.0 percent), but not significantly more ($P=0.13$); and seven case patients reported a history of cirrhosis, which could be confirmed in four from the medical chart. None of these diseases were reported by any of the controls.

Table 3 shows the frequency of appetite-suppressant use and the adjusted odds ratios for primary pulmonary hypertension with all the confounding variables and other risk factors. Thirty case patients (31.6 percent) and 26 controls (7.3 percent) reported using appetite suppressants before their index date, yielding a crude (matched) odds ratio of 7.1 (95 percent confidence interval, 3.7 to 13.9) and an adjusted odds ratio of 6.3 (95 percent confidence interval, 3.0 to 13.2) (Table 3). The odds ratio associated with recent use (in the year before the index date) was 10.1 (95 percent confidence interval, 3.4 to 29.9), and the odds ratio associated with past use was 2.4 (95 percent confidence interval, 0.7 to 8.2). The odds ratio increased sharply with the duration of exposure (use for three months or less, 1.8; use for more than three months, 23.1). The total intake of anorexic drugs was estimated by totaling the reported number of months of use. Figure 1 shows the distribution of such intake for the patients with primary pulmonary hypertension and the controls. Very few controls (0.6 percent) used anorexic agents for a total of 12 months or more, as compared with 12.6 percent of case patients.

When the case patients with cirrhosis, familial pulmonary hypertension, HIV infection, or intravenous drug use and their matched controls were excluded from the analysis, the adjusted odds ratio associated with anorexic-drug use increased to 8.6 (95 percent confidence interval, 3.8 to 19.5). There was no change in the effects of anorexic drugs or other risk factors for primary pulmonary hypertension when alcohol intake was included in the logistic model (odds ratio, 6.3). Among female subjects, 27 patients with primary pulmonary hypertension (40.9 percent) and 25 controls (9.4 percent) had used anorexic drugs (adjusted odds ratio, 7.9; 95 percent confidence interval, 3.5 to 17.5), as compared with 3 male patients with primary pulmonary hypertension (10.3 percent) and 1 male control (1.1 percent) (adjusted odds ratios were not defined for men).

Table 3 also shows the individual drugs used by the case patients and the controls. Dexfenfluramine and fenfluramine were the most commonly used: 22 patients (23.2 percent) and 23 controls (6.5 percent) had used at least one of them; of these subjects, 16 patients (16.8 percent) and 18 controls (5.1 percent) reported not using any other anorexic drug. Amphetamine-like anorexic agents (diethylpropion, clobenzorex, fenproporex, phenmetrazine, or a combination of these) had been used by eight case patients (8.4 percent) and eight controls (2.3 percent), among whom only two case patients and three controls did not also report using a fenfluramine derivative before the index date. Seven patients with primary pulmonary hypertension (7.4 percent) and no controls reported exposure to compound preparations. The content of the compound preparations used by three patients was learned: one contained dexfenfluramine, one contained an amphetamine-like anorexic agent and possibly fenfluramine, and one contained both an amphetamine-like anorexic agent and dexfenfluramine; the preparations also typically contained diuretics, phytotherapy products, thyroid extracts, or a combination of these. Most of the exposure to appetite suppressants occurred in France (22 patients and 22 controls) and Belgium (6 patients and 4 controls). One patient each from the United Kingdom and the Netherlands had used ap-

TABLE 3. USE OF APPETITE SUPPRESSANTS AND ADJUSTED ODDS RATIOS FOR THE RISK OF PRIMARY PULMONARY HYPERTENSION.

VARIABLE	CASE PATIENTS (N=95)	CONTROLS (N=355)	ADJUSTED ODDS RATIO (95% CI)*
	no. (%)		
Definite use of appetite suppressants	30 (31.6)	26 (7.3)	6.3 (3.0–13.2)
Duration of use			
≤3 mo	7 (7.4)	12 (3.4)	1.8 (0.5–5.7)
>3 mo	18 (19.0)	5 (1.4)	23.1 (6.9–77.7)
Indeterminate	5 (5.3)	9 (2.5)	2.6 (0.5–12.6)
Products reported as used†			
Dexfenfluramine	18 (18.9)	22 (6.2)	—
Fenfluramine	6 (6.3)	4 (1.1)	—
Diethylpropion	3 (3.2)	2 (0.6)	—
Clobenzorex	3 (3.2)	6 (1.7)	—
Fenproporex	2 (2.1)	1 (0.3)	—
Phenmetrazine	2 (2.1)	0	—
Compounds	7 (7.4)	0	—
Possible use	3 (3.2)	2 (0.6)	
Use after index date	3 (3.2)	17 (4.8)	
Timing of use‡			
Recent	14 (21.5)	7 (3.0)	10.1 (3.4–29.9)
Past	7 (10.8)	14 (6.0)	2.4 (0.7–8.2)

*Odds ratios were adjusted for systemic hypertension, use of cocaine or intravenous drugs, smoking status, high body-mass index, weight-loss behavior, use of thyroid extracts, and possible exposure to anorexic agents. CI denotes confidence interval.

†Categories shown are not mutually exclusive because patients may have had multiple concomitant or serial exposures.

‡Data are based on appetite-suppressant use in 65 case patients and 234 matched controls. Recent denotes anorexic-drug use within the 12 months before the index date, and past denotes use that ended more than 12 months before the index date.

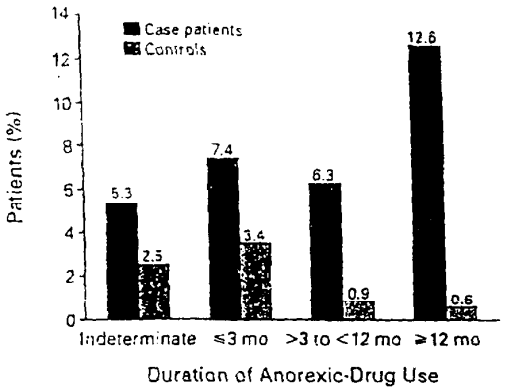

Figure 1. Duration of Exposure to Anorexic Drugs in the Study Patients before the Onset of Symptoms of Primary Pulmonary Hypertension.

petite suppressants. The matched crude odds ratios associated with the use of appetite suppressants were 10.7 in Belgium and 5.9 in France (these ratios could not be calculated in the Netherlands or the United Kingdom). All the patients from the national referral center in France and several Belgian patients were followed, and there was no marked improvement in the condition of those who had used anorexic agents after that use had stopped.

Table 4 shows the frequency of the weight-related confounding variables and the other variables thought to be risk factors for primary pulmonary hypertension, with their corresponding odds ratios (after adjustment for each other and for the use of anorexic agents). High body-mass index, treated systemic hypertension, the use of cocaine or intravenous drugs (in patients without HIV infection), and pregnancy in the year before the onset of symptoms were more frequent in the patients with primary pulmonary hypertension than in the controls, but not significantly so. The case patients used thyroid extracts less often than the controls, but not significantly so. Although smoking was reported significantly more often by case patients than by controls, it was not associated with an increased risk of primary pulmonary hypertension when other covariates were controlled for. The use of oral contraceptives, hashish, and marijuana (data not shown) did not differ between the patients and the controls. When the case patients with HIV, cirrhosis, familial pulmonary hypertension, or intravenous drug use and their matched controls were excluded from the analysis, the effect of the risk factors shown in Table 4 did not differ notably between groups. The adjusted odds ratio associated with obesity was 1.6 (95 percent confidence interval, 0.7 to 3.7) in women.

Incidence Study

In the study of the annual incidence of primary pulmonary hypertension in Belgium, 24 patients were identified over a 24-month period (13 were included in the case–control study and 11 either had died or were identified too late to be included). There were approximately 7 million inhabitants of Belgium 18 to 70 years of age at the time of the study. The annual incidence of primary pulmonary hypertension in this population was 1.7 per million (95 percent confidence interval, 1.0 to 2.4).

DISCUSSION

Our most striking findings concern the use of appetite suppressants as a risk factor for primary pulmonary hypertension, especially use lasting more than three months (odds ratio, 23.1). This is especially important because dexfenfluramine, the main drug involved in this study, was recently approved by the Food and Drug Administration for the long-term treatment of obesity. The risk of primary pulmonary hypertension seems to increase steadily with the quantity of appetite suppressants used, but there has been very little experience with their long-term use in Europe.

We conducted additional analyses to identify potential sources of bias. We investigated whether patients exposed to anorexic agents could have been preferentially included in the study. This phenomenon may not be significant in the United Kingdom and the Netherlands, where anorexic agents were rarely used, or in Belgium, where the number of patients in the incidence study was very close to the

TABLE 4. FREQUENCY OF WEIGHT-RELATED AND OTHER VARIABLES AND ADJUSTED ODDS RATIOS FOR THE RISK OF PRIMARY PULMONARY HYPERTENSION.

VARIABLE	CASE PATIENTS (N=95)	CONTROLS (N=355)	ADJUSTED ODDS RATIO (95% CI)*
	no. (%)		
All patients			
Body-mass index ≥30	34 (35.8)	65 (18.3)	1.9 (1.0–3.6)
Weight-loss behavior	57 (60.0)	178 (50.1)	1.1 (0.6–2.0)
Thyroid-extract use	2 (2.1)	11 (3.1)	0.5 (0.1–2.5)
Systemic hypertension	11 (11.6)	21 (5.9)	2.1 (0.7–6.0)
Use of cocaine or intravenous drugs	4 (4.2)	4 (1.1)	2.8 (0.5–15.7)
Smoking	42 (44.2)	112 (31.5)	1.4 (0.8–2.4)
Female patients†			
Recent pregnancy	5 (7.6)	14 (5.3)	1.9 (0.6–6.0)
Oral-contraceptive use	47 (71.2)	174 (65.7)	1.3 (0.6–3.1)

*Odds ratios are adjusted for appetite-suppressant use. CI denotes confidence interval.

†Data shown are based on 66 case patients and 265 matched controls.

number expected on the basis of earlier figures.[14] In France, only two thirds of the centers contacted agreed to participate in the study. We think it very unlikely that at these centers a significant number of patients, if any, with diagnosed primary pulmonary hypertension might not have been reported, considering all the verification procedures we used. There is no reason to believe that the proportion of patients exposed to anorexic agents would differ in the centers that did not participate. We have been informed that at least five cases of primary pulmonary hypertension diagnosed during the study period in patients who were exposed to derivatives of fenfluramine were reported to the manufacturer by nonparticipating centers. Among the participating centers, the exposure to anorexic agents was similar in the patients originally identified at the national referral center (31 percent) and those identified at all the other French centers combined (37 percent). Also, we obtained data on exposure to anorexic drugs in the 13 patients identified too late to be included in the study and found that it was 31 percent — close to the proportion reported for the patients who were included. Sixty-two percent of the patients did not report any use of anorexic agents, as is consistent with the fact that anorexic agents are obviously not the only possible cause of this disease.

There could be another selection bias if persons with primary pulmonary hypertension who used anorexic agents were more likely to have their disease recognized than other patients. To explore this potential bias, we examined the time between the appearance of the first symptoms and the diagnosis and found that it did not differ significantly between the case patients who used anorexic agents and those who did not (16.8 and 17.6 months, respectively). We also compared the degree of dyspnea at the time of diagnosis and found that it was more often severe (New York Heart Association class III or IV) in case patients who used anorexic agents (89.7 percent) than in those who did not (56.6 percent), whereas the reverse would be expected if there were a preferential bias based on the diagnosis. (This study was done only among patients whose index dates were later than August 1, 1989.)

We also examined potential sources of misclassification of the exposure to anorexic agents. Patients with primary pulmonary hypertension might be more likely to remember using anorexic agents than controls (recall bias). On the basis of sales figures, we estimated a priori that 5 percent of the controls would have exposure to a derivative of fenfluramine,[14] and we found that 6.2 percent actually had such exposure. The accuracy of the index date was another source of concern, since the development of dyspnea is often insidious. To explore this matter, we recalculated the odds ratios with the index dates moved back to 12 months before the reported dates and found that the odds ratio associated with the use of anorexic agents was 7.4 — higher than the original odds ratio (6.3). Exposure after the original index date was slightly less frequent in the case patients than in the controls. All this rules out a "protopathic" (reverse causality) bias. We could not verify the actual content of most of the so-called appetite-suppressant compound preparations, but in the three instances in which we could do so, we found that they did contain anorexic agents. "Possible exposure" to anorexic agents was more often found in case patients than in controls.

We considered whether the association between the use of appetite suppressants and primary pulmonary hypertension could be explained by the confounding effect of obesity or that of any hidden factor associated with obesity. The odds ratio for anorexic agents was similar whether or not the logistic-regression models were adjusted for high body-mass index. The odds ratio for the interaction between obesity and appetite-suppressant use was 1.0 (95 percent confidence interval, 0.2 to 3.5). Therefore, the effect of anorexic agents was the same whether patients had a high body-mass index or not. Neither weight-loss behavior of another type nor the use of thyroid extracts was positively associated with the risk of primary pulmonary hypertension, as would have been expected if obesity accounted for the odds ratio observed for anorexic agents.

We believe that the association between anorexic agents and primary pulmonary hypertension is due to neither bias nor chance. Our findings are consistent with observations in the 1960s of an association of primary pulmonary hypertension with the use of aminorex fumarate[11] and of more recent associations with fenfluramine derivatives, other anorexic agents, or related products.[11-13,16-18] The consistency of our observations with previous findings, the strength of the association, the fact that it increases with longer use, and the fact that it is stronger with recent use than with past use all favor a causal relation. It is also worth noting that cases have been described in which the disease regressed after exposure to fenfluramine ended.[17] Susceptibility factors are also likely to play a part, considering the rarity of primary pulmonary hypertension. The results apply mainly to derivatives of fenfluramine, which were used by 90 percent of the subjects who named an individual anorexic agent and were contained in all the preparations whose actual content was determined. The role of other amphetamine-like anorexic agents is unclear, and such agents were rarely used alone.

How fenfluramine and dexfenfluramine may lead to pulmonary hypertension is unknown. Hypotheses have been put forward that implicate serotonin,[19] a pulmonary vasoconstrictor, a direct vasoconstrictor effect through potassium-channel blockade[20] (an effect that has also been shown to occur with amino-

rex), and pulmonary vasoconstriction,[21] but these hypotheses remain speculative.

This international epidemiologic study of primary pulmonary hypertension confirms the clinical features of the disease as described in the National Registry of Primary Pulmonary Hypertension[2] and several case series.[15,22] The severity of dyspnea at the time of diagnosis was consistent with the long delay between the first symptoms and diagnosis, a finding similar to that observed in the registry.[2] Efforts to shorten the delay could be valuable, since treatment has recently been shown to be effective in some patients.[23,24]

Our results also confirm the role of several previously described risk factors for pulmonary hypertension, including HIV infection[8,25] and cirrhosis.[4,5] Because of simultaneous or multiple exposures, the role of intravenous drug use could not be examined separately from that of cocaine use, but both were used more frequently by the patients with primary pulmonary hypertension than by the controls. Primary pulmonary hypertension has previously been observed in infants born to mothers with a history of cocaine abuse[7] and in users of related drugs.[26,27] Pulmonary hypertension associated with intravenous drug use may also be due to the embolism of talc or other foreign substances. Recent pregnancies[6] and treated systemic hypertension appeared to be more frequent in the case patients than in the controls, but the study did not have sufficient power to be conclusive in this regard. We could not confirm the previously reported suspicion of an association with oral-contraceptive use.[9,10] Obesity, which was marginally associated with the risk of primary pulmonary hypertension in this study, has not been previously reported as a risk factor. A subject's report of obesity may have been associated with use of anorexic agents that the subject did not report. If so, the appearance of an effect of obesity on the risk of primary pulmonary hypertension simply reflects the harmful effects of small amounts of unrecorded drug use.

In conclusion, the annual incidence of primary pulmonary hypertension estimated from this study is very low — on the order of 1 case per 500,000 inhabitants. The corresponding absolute risk for obese persons who use anorexic agents for more than three months would be more than 30 times higher than for nonusers. It is not known to what extent the risk continues to increase with longer use, because the experience with long-term use of anorexic agents has been extremely limited. We recommend active surveillance of the use of these drugs, especially if long-term use is planned.

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APPENDIX

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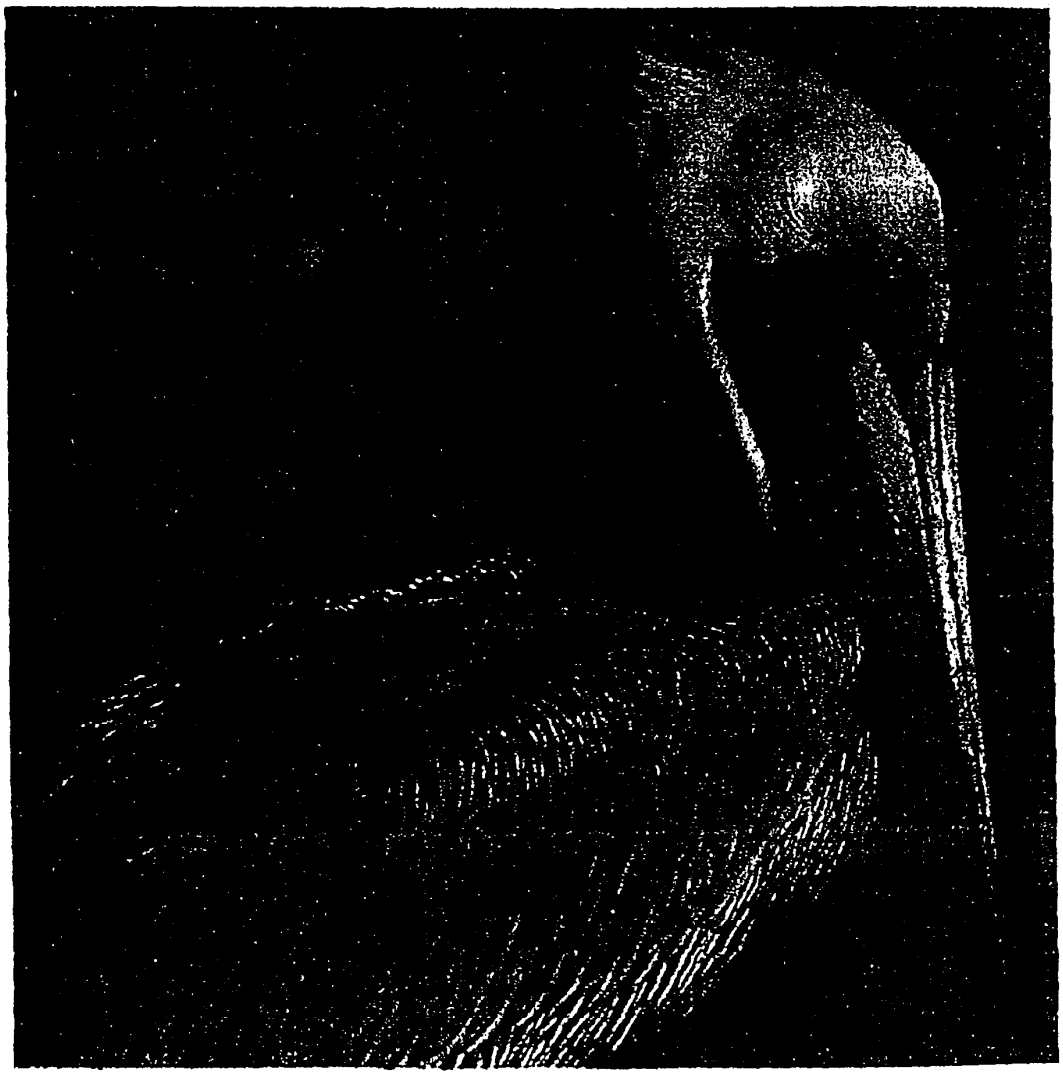

Brown Pelican — B. Leonard Holman, M.D.

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Pulmonary Vasculitis and Primary Pulmonary Hypertension

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INTRODUCTION

Disorders affecting the pulmonary circulation comprise a heterogeneous group without unifying or characteristic etiologic, physiologic, or pathologic features. Many of these diseases, however, share a variety of clinical manifestations that are the result of the disruption of the delicate interface between the ventilation and perfusion components of the lung and the impact of altered pulmonary vascular dynamics on the function of the right ventricle. This chapter addresses two forms of pulmonary vascular disease: the vasculitides and primary pulmonary hypertension. Other pulmonary vascular disorders or complications that are discussed in this section include thromboembolism in Chapter 53, arteriovenous fistulas and other malformations in Chapter 55, pulmonary edema and acute lung injury in Chapter 56, and cor pulmonale in Chapter 57.

PULMONARY VASCULITIS

The vasculitides are a diverse group of disorders that are characterized by inflammation within and surrounding the blood vessel walls.[1] When the inflammation leads to destruction of the blood vessels, the process is often referred to as a necrotizing vasculitis.[2] Many investigators restrict application of *vasculitis* and *angiitis* to only those situations in which necrosis is evident.[3] In this chapter, the terms *pulmonary vasculitis* and *pulmonary angiitis* will be applied to inflammatory disorders of the pulmonary blood vessels with or without necrosis.

Classification

Vasculitis first was identified as a distinct clinicopathologic entity in 1837 by Schönlein[4] in describing the disease now known as anaphylactoid purpura. Kussmaul and Maier[5] in 1866 described the syndrome of polyarteritis nodosa in a patient with fever, muscle weakness, gastrointestinal symptoms and renal disease in whom a diffuse necrotizing vasculitis was found at autopsy. Over the following years this term was used in patients with a variety of vasculitides attributed to hypersensitivity reactions to drugs, infectious antigens, rheumatic diseases, and other disorders.

A number of attempts have been made to classify and organize the pulmonary vasculitides.[6–10] However, these efforts have lacked consensus because these conditions overlap considerably in clinical manifestations and morphologic features and because their causes are unknown. Recently, the American College of Rheumatology proposed diagnostic criteria for various vasculitides, based on a study of 807 patients who met specific criteria established for the diagnosis of several types of vasculitis.[11–19] Subjects with vasculitis secondary to underlying connective tissue diseases were excluded from this study. These criteria may prove

useful to clinicians, both for the diagnosis and the classification of vasculitic entities.

Epidemiology

Pulmonary vasculitis is an uncommon condition despite the relative frequency of collagen vascular diseases and other conditions that may be associated with vasculitis in the general population. Even Wegener's granulomatosis, perhaps the best known pulmonary vasculitis, is rarely encountered in clinical practice; Fauci and Wolff[20] noted that only 200 cases of this disorder had been reported up to 1967, although the true incidence probably was higher. The incidence of other pulmonary vasculitides for the most part remains unknown.

Pulmonary vasculitis can occur in persons of all ages, although anaphylactoid purpura is more common among children, and the granulomatous vasculitides usually affect patients in their fifth and sixth decades.[10] Vasculitis associated with collagen vascular disease is described most often among women, as is necrotizing sarcoid angiitis and granulomatosis. On the other hand, Wegener's granulomatosis, lymphomatoid granulomatosis, and allergic granulomatosis and angiitis are reported most frequently in men. Familial and racial predispositions are noted primarily in patients with the collagen vascular disorders and giant cell arteritis.

Pathology

Inflammation, frequently extending through all layers of the blood vessel wall, is the hallmark of pulmonary vasculitis. With the exception of bronchocentric granulomatosis, this process is angiocentric in that it appears to originate in the blood vessels, although surrounding tissues frequently are involved. Arteries and veins of all sizes may be involved, and capillaritis may accompany these pathologic changes in some conditions. Fibrinoid necrosis often accompanies the inflammation, as do intimal proliferation and perivascular fibrosis. Because these processes may cause obstruction of the blood vessels, pulmonary vasculitis often leads to obliterative pulmonary vascular disease. Secondary thrombosis may also contribute to vascular obstruction in this setting.

The inflammatory cells responsible for pulmonary vasculitis include neutrophils, normal and abnormal lymphocytes, eosinophils, monocytes, macrophages, histiocytes, plasma cells, multinucleated giant cells, and combinations thereof. Vasculitis is called leukocytoclastic if neutrophils predominate and granulomatous if lymphocytes predominate. However, lymphocytes may be abundant in areas of leukocytoclastic vasculitis if the process is more than 24 hr old, just as mononuclear cells, histiocytes, and multinucleated giant cells may outnumber lymphocytes in the later stages of granulomatous vasculitis.[2, 21]

Pathogenesis and Etiology

Despite their differences, the pulmonary vasculitides appear to share a common immunopathogenesis. This concept is supported by several observations.[1-3] (1) Leukocytoclastic vasculitis, polyarteritis nodosa, and essential mixed cryoglobulinemia may occur with illnesses such as hepatitis B infection that are associated with immune complex deposition within blood vessel walls. (2) Vasculitis may be a component of collagen vascular disorders in which immunologic pathogenetic mechanisms are well accepted. (3) Patients with vasculitis may manifest serologic abnormalities associated with immunodysfunction, including the presence of rheumatoid factor, cryoglobulinemia, hyperglobulinemia, hypocomplementemia, and circulating immune complexes. (4) Vasculitis may be temporally associated with infections, drug ingestion, and other kinds of antigen exposure. (5) The upper and lower airway involvement with granulomatous vasculitis in particular suggests that foreign antigens may enter the body via the respiratory tract. (6) Finally, these and other vasculitides frequently respond to immunosuppressive or cytotoxic therapy.

Many investigators believe that pulmonary vasculitis is caused by a type III hypersensitivity reaction involving the deposition of immune complexes in blood vessels.[1] Although the antigens responsible for this process rarely have been identified, streptococcal M protein, hepatitis B surface antigen, and *Mycobacterium tuberculosis* have been found in or near the site of vascular inflammation. Immunoglobulins M, G, and A and complement breakdown products also have been localized in the blood vessels of patients with leukocytoclastic vasculitis, polyarteritis nodosa, and collagen vascular disorders.[2] How the antigens and antibodies come together is not certain; the antigens may bind to vascular basement membranes, diffuse into the blood vessels from surrounding tissues, or travel in the bloodstream. At any rate, a significant excess of antigen over antibody is necessary to create immune complexes that are small enough to elude the reticuloendothelial system yet insoluble enough to deposit in blood vessel walls.[10]

The blood vessels also must be predisposed to accept immune complexes. Such acceptance probably involves local vasodilation and increased vascular permeability that are mediated by vasoactive amines released by platelets, mast cells, and basophils. After the immune complexes are deposited, complement activation is thought to occur by either the direct or the alternate pathway.[1] Certain complement components, such as C3a, cause further

vasodilation and increased vascular permeability, whereas C5a and its breakdown product, C5a des arginine, attract neutrophils. The neutrophils then are stimulated to ingest the immune complexes and to release toxic enzymes and oxygen radical species.[3]

Although this sequence can be implicated in leukocytoclastic vasculitis and polyarteritis nodosa, it may not apply to granulomatous vasculitis, in which immune complex deposition rarely is demonstrated and complement levels are increased. These facts and the characteristic histology of granulomatous vasculitis have prompted the hypothesis that cell-mediated immune events are involved in this condition. The involvement may be secondary in that it follows immune complex deposition that cannot be detected. Whether such deposition occurs or not, sensitized T lymphocytes are assumed to contact antigens and either cause direct cytotoxicity or recruit mononuclear cells to the site. These mononuclear cells in turn become activated macrophages that release lysosomal enzymes. At the same time, some of the cells evolve into the histiocytes and multinucleated giant cells that participate in granuloma formation.[1]

Symptoms

In general, systemic symptoms more commonly accompany the vasculitides that produce minimal pulmonary involvement, whereas respiratory complaints predominate among the vasculitides that primarily involve the lungs.[1-3, 10] For example, the initial manifestations of leukocytoclastic vasculitis include fever, malaise, arthralgias, and skin lesions. Symptoms referable to the skin and joints also are seen among patients with collagen vascular disorders and polyarteritis nodosa.[22] In contrast, dyspnea and cough frequently occur among patients with granulomatous vasculitis; symptoms related to the upper airways, including sinus pain and epistaxis, suggest Wegener's granulomatosis and lymphomatoid granulomatosis.[8] Hemoptysis also is reported in these disorders and may be massive in patients with pulmonary artery aneurysms[3] or diffuse capillaritis. Periodic dyspnea or a history of asthma is characteristic of allergic granulomatosis and angiitis (Churg-Strauss syndrome).[15, 23]

Physical Findings

The physical findings generally parallel the symptoms of patients with pulmonary vasculitis. For example, purpura, bullae, and dermal ulcers may be evident in patients with leukocytoclastic vasculitis.[3] Joint deformity is suggestive of rheumatoid arthritis, whereas thickening of the skin and Raynaud's phenomenon may accompany progressive systemic sclerosis.[22] Erosions of the nose and upper airways are characteristic of Wegener's granulomatosis and lymphoid granulomatosis; proptosis caused by orbital pseudotumors and sclerouveitis also are seen in the former condition.[8] Iritis and oral and genital ulcers are hallmarks of Behçet's syndrome. Peripheral nerve lesions are especially common in polyarteritis nodosa. Central nervous system lesions are described in the giant cell arteritides and other conditions.[1] Patients with eosinophilia-myalgia syndrome frequently manifest many of the features of systemic sclerosis; in addition, they may have peripheral neuropathy, myositis, and fasciitis.[24, 25]

Diagnosis

Despite certain characteristic presentations, the vasculitides rarely can be diagnosed solely on clinical grounds. Potentially helpful laboratory studies include the erythrocyte sedimentation rate, which usually is elevated in giant cell arteritis, and the differential white blood cell count, which is normal in most patients with vasculitis but may show an eosinophilia in patients with allergic granulomatosis and angiitis[14] or eosinophilia-myalgia syndrome.[24, 25] An elevation of immunoglobulins, a decrease in total complement and complement components, and the presence of circulating immune complexes may be present in leukocytoclastic vasculitis.[3] Determinations of rheumatoid factor levels, antinuclear antibody patterns, and antineutrophil cytoplasmic antibodies[26] are useful in the differential diagnosis of collagen vascular diseases and Wegener's granulomatosis, respectively.

Leukocytoclastic vasculitis and the vasculitis associated with collagen vascular disorders characteristically cause patchy infiltrates when they involve the lungs. Pleural effusions have been reported among patients with anaphylactoid purpura, collagen vascular disease,[10] and Churg-Strauss syndrome.[27] The angiocentric granulomatous vasculitides usually cause patchy infiltrates or pulmonary nodules; the latter often are bilateral and may cavitate.[8, 10] Bronchocentric granulomatosis, on the other hand, is associated with fleeting infiltrates similar to those seen in allergic bronchopulmonary aspergillosis and mucoid impaction.[28] Visualization of the upper airways using plain roentgenograms or computerized tomography is often employed in the evaluation of Wegener's granulomatosis and lymphoid granulomatosis.[8] Angiographic studies frequently are undertaken in patients with polyarteritis nodosa, giant cell arteritis, and Takayasu's arteritis.

Hypoxemia, often in concert with hypocapnia and chronic respiratory alkalosis, is present in many patients whose lungs are involved with vasculitis.[3] Pulmonary function tests usually reveal normal or

mildly reduced flow rates and lung volumes, unless obstructive or restrictive disorders coexist. In 1968 Nadel and associates[29] reported that the diagnosis of pulmonary vascular obstruction was suggested by a decreased diffusing capacity for carbon monoxide, an increased dead space to tidal volume ratio, and an increased alveolar to arterial P_{O_2} difference at rest. These abnormalities have been shown to worsen during progressive exercise in the same general group of patients.[30] However, few static or dynamic studies of pulmonary function have been reported in patients with the less common vasculitides.

Given the general lack of clinical experience with pulmonary vasculitis, a tissue biopsy usually is required for diagnosis. Skin biopsy is the preferred initial approach in patients with lesions attributable to granulomatous vasculitis, leukocytoclastic vasculitis, or polyarteritis nodosa.[3] If this approach is not helpful, upper airway biopsy may be revealing in patients suspected of having Wegener's granulomatosis or lymphomatoid granulomatosis. Renal biopsy is not recommended in patients with the former condition, because granulomas usually are not present; the lungs therefore are a preferred biopsy site.[8] Transbronchial biopsy frequently is not helpful in the evaluation of pulmonary vasculitis, owing to the small amount of tissue obtained. As a result, many investigators recommend open lung biopsy.[10] This recommendation needs to be reconsidered in the light of the recent information that nearly all patients (> 90%) with active Wegener's granulomatosis have a positive test for cytoplasmic (as opposed to perinuclear) antineutrophil cytoplasmic antibodies (ANCA).[30a] Current opinion holds that ANCA antibodies are a highly specific objective marker for the important group of vasculitides that includes Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome, and pauci-immune glomerulonephritis with or without pulmonary hemorrhage.[30b] Temporal artery biopsy is employed in establishing the diagnosis of temporal arteritis.

Treatment

Leukocytoclastic vasculitis often is self-limited and responds to removal of the offending antigen. A trial of corticosteroids may be used if extensive disease or pulmonary complications such as hypoxemia are present, although their general utility is unclear.[2] Corticosteroids also have been used for allergic granulomatosis and angiitis, necrotizing sarcoid granulomatosis, bronchocentric granulomatosis, eosinophilia-myalgia syndrome, and giant cell arteritis.[3, 10] Failure to respond to corticosteroids usually leads to cytotoxic therapy, especially when lung and renal involvement is severe. Wegener's granulomatosis, in particular, may respond dramatically to cyclophosphamide, as will be discussed.[31] Cyclophosphamide and other cytotoxic agents have been used in patients with lymphomatoid granulomatosis, allergic granulomatosis and angiitis, polyarteritis nodosa, and vasculitis associated with collagen vascular disorders.[1-3, 10]

Specific Disorders

Although there is considerable overlap among the various disorders that constitute the continuum of pulmonary vasculitides, numerous entities have been recognized as having certain clinical and pathologic specificity. In this section each of the specific disorders listed in Table 54–1 will be briefly described. Many of these diseases, particularly the connective tissue diseases (also known as collagen vascular disorders), also may present with manifestations of infiltrative and interstitial involvement of the lung parenchyma. For further information about these aspects of the disorders, the reader is referred to Chapter 60.

Wegener's Granulomatosis. Wegener[32] in 1936 described the clinical syndrome that now bears his name and that consists chiefly of necrotizing granulomatous vasculitis of the upper and lower respiratory tract and glomerulonephritis. He considered the syndrome a variant of polyarteritis nodosa and called it rhinogenic granuloma, with reference to the prominent nasal and paranasal involvement.[33] Although clinical attention usually is focused on the respiratory and renal lesions of Wegener's granulomatosis, the disease also may involve the eyes, ear, heart, skin, joints, and peripheral and central nervous systems.[8, 20, 30a, 33, 34] The cause of Wegener's granulomatosis is unknown. However, an immu-

Table 54–1. Classification of Pulmonary Vasculitides

Specific Disorders
Granulomatous vasculitis
Wegener's granulomatosis
"Limited" Wegener's granulomatosis
Lymphomatoid granulomatosis
Allergic granulomatosis and angiitis (Churg-Strauss syndrome)
Necrotizing sarcoid granulomatosis
Bronchocentric granulomatosis
Leukocytoclastic vasculitis
Anaphylactoid purpura (Henoch-Schönlein purpura)
Essential mixed cryoglobulinemia
Vasculitis associated with collagen vascular disorders
Rheumatoid arthritis
Systemic lupus erythematosus
Progressive systemic sclerosis
Polymyositis and dermatomyositis
Mixed connective tissue disease
Classic polyarteritis nodosa
Giant cell (temporal) arteritis
Takayasu's disease
Behçet's syndrome
Hughes-Stovin syndrome
Eosinophila-myalgia syndrome

nopathogenesis is supported by the finding of hypergammaglobulinemia and circulating antibodies in patients with the disorder, in addition to their dramatic response to cytotoxic therapy.[31, 34, 35]

Of the vasculitides that typically affect the lungs, Wegener's granulomatosis is the most common, comprising approximately 10% of all systemic vasculitides clinically diagnosed.[13] Wegener's granulomatosis may affect persons of all ages but is most common in middle-aged patients, predominantly men.[8, 13, 36] Sinusitis is the most frequent presenting symptom, followed by fever, arthralgias, cough, rhinitis, hemoptysis, otitis, and ocular inflammation.[37] Upper respiratory tract involvement may include destruction of tissue and bone and secondary bacterial infection; this may lead to confusion with midline granuloma, a necrotizing and ulcerating granulomatous process usually limited to the nose and face.[38] Pulmonary involvement ranges from minimal to life-threatening. The chest roentgenogram is abnormal in two thirds of patients, with infiltrates occurring most frequently (63%), followed by nodules (31%), infiltrates with cavitation (8% to 10%), and nodules with cavitation (10%).[13, 39, 40] Bilateral abnormalities occur with nearly equal frequency as unilateral abnormalities. Atelectasis due to endobronchial obstruction and pleural disease with thickening or effusions also have been reported.[41] Lung biopsy usually reveals parenchymal necrosis, granulomatous inflammation accompanied by an infiltrate consisting of a mixture of neutrophils, lymphocytes, plasma cells, eosinophils, and histiocytes, and vasculitis with blood vessel obstruction and bland infarcts (Fig. 54–1). Capillaritis can be seen in almost one third of patients and is a significant cause of hemoptysis.[42] Less commonly, interstitial fibrosis, acute and chronic bronchiolitis, bronchiolitis obliterans, lipoid pneumonia, and tissue eosinophilia can be seen.[43]

In 1985 van der Woude and associates[44] reported a high sensitivity of antineutrophil cytoplasmic autoantibodies (ANCA) for active Wegener's granulomatosis, and suggested that ANCA may be useful as a marker of disease activity. Although ANCA activity may be detected in other vasculitides, its presence is most strongly associated with Wegener's granulomatosis, and the cytoplasmic staining pattern is reported to be present in over 90% of patients with untreated active disease.[45–45b] The rate of positivity declines substantially when the disease is in remission but the test is not sufficiently sensitive to serve as a guide to therapy.[30a]

In the past, patients with Wegener's granulomatosis died within months or a few years of diagnosis because of disseminated vasculitis and renal failure.[33] Corticosteroids rarely affected this prognosis, but it was altered considerably after the advent of cytotoxic drugs. The cytotoxic agent of choice today is cyclophosphamide in a dosage of 1 to 2 mg/kg per day, either alone or in combination with lower doses of corticosteroids, continued for at least 1 year after a decline in disease activity.[46] From 75% to 90% of patients treated with this regimen experience a complete remission. Recently, the antimicrobial agent trimethoprim-sulfamethoxazole has also been reported to produce improvement in several patients,[47] although similar benefits were not observed in another clinical trial.[30a]

"Limited" Wegener's Granulomatosis. Carrington and Liebow[48] in 1966 described 16 patients with clinical and morphologic features of Wegener's granulomatosis but without glomerulonephritis. There was no evidence of asthma or eosinophilia to suggest allergic granulomatosis and angiitis in these patients. Six of them died of progressive pulmonary disease, but another six survived for 12 months or more without immunosuppressive or cytotoxic therapy. The favorable outcome subsequently was confirmed in other studies,[49] and "limited" Wegener's granulomatosis is now considered by some authors to represent a disease distinct from "classic" Wegener's granulomatosis. However, others believe

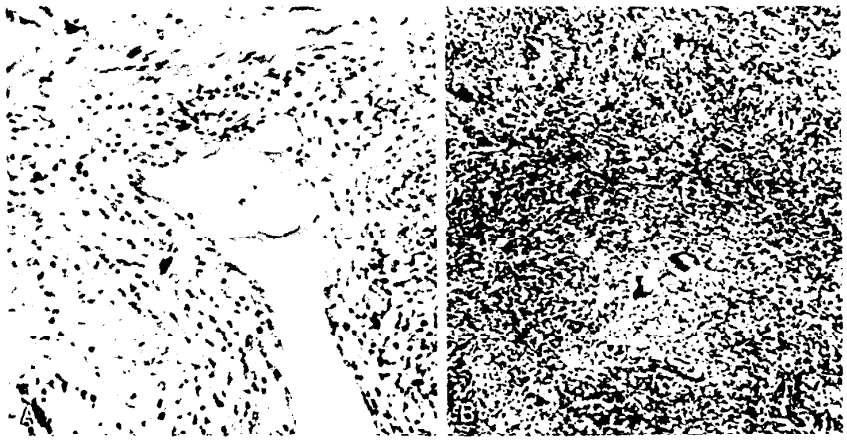

Figure 54–1. Hematoxylin and eosin stains of autopsy specimens from a patient with Wegener's granulomatosis. *A*, Angiitis in wall of pulmonary blood vessel. *B*, At higher power, note granulomatous inflammation with histiocytes and giant cells. (Courtesy Martha L. Warnock, M.D.; reproduced with permission from Luce, J. M.: Vasculitis, primary pulmonary hypertension, and arteriovenous fistulas. *In* Murray, J. F., Nadel, J. A. [eds.]: Textbook of Respiratory Medicine. Philadelphia, W. B. Saunders, 1988.)

that limited Wegener's granulomatosis represents an earlier form of the disease rather than a separate clinical entity and advocate aggressive treatment using the same strategy employed for classic Wegener's granulomatosis.

Lymphomatoid Granulomatosis. In 1972 Liebow and associates[50] first described a unique form of pulmonary angiitis and granulomatosis that they called lymphomatoid granulomatosis. The disorder is characterized histologically by an angiocentric and angiodestructive infiltration of the upper and lower respiratory tract, skin, central nervous system, and kidneys by lymphoblasts, plasma cells, histiocytes, and large atypical lymphocytes with abnormal mitotic activity.[50, 51] Although the histogenesis of the disease is uncertain, immunologic markers have indicated a predominance of T lymphocytes in one well studied patient.[52]

Although the original report of lymphomatoid granulomatosis cited only 40 patients, Katzenstein and colleagues[51] in 1979 identified and reported on 157 patients in Liebow's consultation files. The 150 patients whose ages were known ranged from 7 to 85 years, with a mean age of 48 years. Men outnumbered women almost two to one. In contrast to persons with Wegener's granulomatosis, the patients with lymphomatoid granulomatosis usually presented with lower respiratory tract symptoms, including chest pain, dyspnea, and cough. Their chest roentgenograms, however, were indistinguishable from those of patients with Wegener's granulomatosis. Central nervous system involvement also was common, but renal disease was uncommon despite autopsy evidence of glomerulonephritis.

Several of the patients with lymphomatoid granulomatosis in Katzenstein's series had preexisting lymphomas, and lymphomas eventually developed in another 16%.[51] The median survival of all patients was 17 months despite immunosuppressive or cytotoxic therapy, with death usually due to progressive pulmonary or central nervous system involvement. In a prospective series collected by Fauci and associates,[53] one half of the patients who received daily cyclophosphamide and every-other-day corticosteroids enjoyed remissions lasting an average of 4 years. However, virtually all the patients who did not achieve remissions eventually developed lymphomas. These findings and their own experience led DeRemee and coworkers[54] to classify lymphomatoid granulomatosis as a malignant lymphoproliferative disorder. Colby and Carrington[55] agreed with this hypothesis and speculated that lymphomatoid granulomatosis probably is a lymphoma whose malignant nature may be obscured by the accompanying polymorphous infiltration.

Israel and colleagues[56] and Saldana and associates[57] have argued that pulmonary angiitis and granulomatosis comprise three predominant types: a lymphocyte-depleted type (corresponding to classic and limited Wegener's granulomatoses), a malignant lymphoproliferative type (corresponding to lymphomatoid granulomatosis), and a benign lymphocytic type (a previously unnamed entity). Their patients with benign lymphocytic angiitis and granulomatosis manifested a polymorphous but histologically benign lymphocytic infiltrate with a mild-to-moderate vasculitis and little or no tissue necrosis. These patients also had consistent responses to chlorambucil. Nevertheless, two patients who appeared to have a benign process eventually developed fatal lymphomatoid granulomatosis. Because of this, benign lymphocytic angiitis and granulomatosis are best considered not as separate entities but rather as one end of a spectrum of disease.[58]

Allergic Granulomatosis and Angiitis (Churg-Strauss Syndrome). In 1951, Churg and Strauss[23] reported 13 cases of severe asthma associated with fever and hypereosinophilia. Pathologically, there were granulomatous extravascular lesions and inflammatory, granulomatous, and necrotizing vascular changes in the small arteries and veins of the lungs, heart, pancreas, spleen, kidneys, and skin. Although most of the patients had been assumed to have polyarteritis nodosa, Churg and Strauss[23] believed that the pathologic findings suggested the presence of a distinct clinical process. Although the cause of this disease remains unknown, an immunologic basis is supported by the presence of elevations in immunoglobulins and circulating immune complexes in many patients.[15, 59]

Allergic granulomatosis and angiitis, or the Churg-Strauss syndrome, primarily affects middle-aged men with current or previous asthma. The lungs, peripheral nerves, skin, heart, and viscera are the most commonly injured organs.[15] Renal disease is infrequent, but the prostate and lower urinary tract may be involved.[60, 61] Unlike Wegener's granulomatosis, Churg-Strauss syndrome is characterized by peripheral eosinophilia, which usually exceeds 10% of the peripheral white blood cell count.[15] Plain chest roentgenograms most often reveal patchy infiltrative or nodular densities. Treatment has included corticosteroids, azathioprine, or cyclophosphamide. Before the availability of corticosteroids, Churg-Strauss syndrome was frequently a rapidly progressive disease. However, recent studies suggest that most patients respond favorably to therapy: none of the 20 patients reported in the American College of Rheumatology registry died as a result of the syndrome.[15]

Necrotizing Sarcoid Granulomatosis. Liebow[8] in 1973 introduced the term necrotizing sarcoid granulomatosis to describe 11 patients with (1) histologic evidence of confluent granulomas similar to those seen in sarcoidosis, in association with a minimally necrotic granulomatous vasculitis involving pulmonary arteries and veins; (2) pulmonary nodules or infiltrates usually in the absence of bilateral hilar lymphadenopathy; and (3) a benign clinical course

with or without the use of corticosteroids. These histologic and roentgenographic characteristics suggested that necrotizing sarcoid granulomatosis was a variant of angiocentric granulomatosis with sarcoidlike features. However, the clinical characteristics favored the concept that necrotizing sarcoid granulomatosis was a variant of sarcoidosis.

Subsequent studies[62-64] have supported the latter concept and have confirmed that necrotizing sarcoid granulomatosis is a comparatively benign condition. Indeed, Churg and colleagues[65] proposed that this entity is the same as or similar to nodular sarcoidosis as described by Sharma and coworkers[66] and Onal and associates.[67] Why necrotizing sarcoid granulomatosis includes a vasculitic component is not understood. Nevertheless, the relative lack of necrosis, the female preponderance, and the likelihood of spontaneous clinical and roentgenographic remission emphasize that this condition differs from the other granulomatous vasculitides.

Bronchocentric Granulomatosis. Liebow[8] described bronchocentric granulomatosis as a disease in which the lower airways were invaded by lymphocytes and plasma cells and ultimately were ulcerated and destroyed. Although adjacent arteries and veins could be injured in the process, their involvement was more or less incidental, unlike that found in angiocentric disorders such as Wegener's granulomatosis. Bronchocentric granulomatosis appeared to affect primarily persons with asthma and produced infiltrates, nodules, or areas of atelectasis on the chest roentgenogram. Yet despite its roentgenographic manifestations and disturbing histologic picture, the disease often caused few respiratory symptoms. Furthermore, it lacked the common extrapulmonary manifestations of other vasculitides.

Katzenstein and associates[28] subsequently updated Liebow's original cases and described other patients with bronchocentric granulomatosis. Approximately one half of the patients in their series had asthma along with eosinophilia and serologic evidence of exposure to *Aspergillus* species and other fungi. *Aspergillus* was recovered from the sputa of several patients, and eosinophils and degraded fungal hyphae were present within necrotizing granulomas in their lungs. These findings and the clinical and roentgenographic similarities among bronchocentric granulomatosis, allergic bronchopulmonary aspergillosis, and mucoid impaction of the bronchi led the investigators to suggest that all three disorders represented hypersensitivity reactions to fungi. Yet bronchocentric granulomatosis occurred without serologic or histologic evidence of allergy in the other half of the patients they reviewed as well as in patients from other series.[68, 69] Although immunopathogenic mechanisms are suspected in these patients, the antigen responsible for their illness has not been identified.

Leukocytoclastic Vasculitis. This type of vasculitis is a systemic disease that involves arterioles, venules, and capillaries in the skin and other organs. It also has been called hypersensitivity vasculitis, allergic vasculitis, and necrotizing vasculitis.[2, 70] The term *leukocytoclastic* is preferred because it describes the neutrophilic infiltration characteristic of the disorder. Leukocytoclastic vasculitis is manifested clinically by palpable purpura of the lower extremities. Other cutaneous lesions include nodules and necrotic ulceration.[70] Eye, joint, gastrointestinal, peripheral and central nervous system, and pulmonary involvement also have been reported, and leukocytoclastic vasculitis may cause respiratory failure.[10]

Leukocytoclastic vasculitis has been observed after infections with streptococci, *M. tuberculosis*, and hepatitis B virus.[2, 71] It also is associated with several drugs, including sulfa compounds and penicillin, and may accompany malignancies such as chronic lymphocytic leukemia, lymphoma, and multiple myeloma.[3] Leukocytoclastic vasculitis presumably represents a response to a wide variety of antigens. This is supported by the finding in affected patients of immunoglobulins and complement components in vessel walls of cutaneous lesions and normal skin.[72]

Anaphylactoid Purpura. Anaphylactoid purpura (Henoch-Schönlein syndrome) is a form of leukocytoclastic vasculitis that has been reported primarily in infants and young children.[16, 73] However, adults may also develop the disease.[74] It commonly follows an upper respiratory infection and manifests as a triad of purpura, arthritis, and abdominal pain. Renal involvement may range from hematuria and other abnormalities of the urinary sediment to severe glomerulonephritis and renal failure. Respiratory tract disease occurs only rarely[10, 16] and consists of alveolar hemorrhage and patchy perihilar infiltrates. Elevated serum IgA- and IgG-containing complexes are often observed in adults with this disease, and most patients have IgA deposition in the kidneys and skin detected by immunofluorescence microscopy. These findings suggest that the disease may represent an immunologic response to a previous infection.[1]

Essential Mixed Cryoglobulinemia. This disease is characterized by recurrent episodes of purpura, weakness, arthralgias, and multiorgan involvement in persons with elevated serum cryoglobulins with rheumatoid factor activity. The histologic picture is that of a leukocytoclastic vasculitis; immunoglobulins and complement components may be found in blood vessels and along the glomerular basement membrane.[2] Bombardieri and associates[75] described lung involvement in 23 patients with essential mixed cryoglobulinemia, only half of whom had serologic evidence of exposure to hepatitis B virus. Most of the patients were hypoxemic, had decreased expiratory flows at low lung volume, and

Figure 54–2. Frontal and lateral chest roentgenograms of 24-year-old woman with pulmonary hypertension associated with the CREST syndrome showing dilated pulmonary outflow tract and widened cardiac silhouette from right ventricular enlargement.

manifested mild inhomogeneity on regional lung perfusion scanning. Although the last test suggested vascular involvement, pathologic studies were not performed.

Rheumatoid Arthritis. Rheumatoid arthritis is a systemic disease characterized by inflammation of the peripheral joints and other organs. The common pleuropulmonary manifestations include pleurisy with or without effusion, necrobiotic nodules (nonpneumoconiotic intrapulmonary nodules), Caplan's syndrome (rheumatoid pneumoconiosis), diffuse interstitial disease, and pulmonary vasculitis and hypertension.[22, 76] The last condition is extremely uncommon; two patients alleged to have rheumatoid vasculitis of the lung[77, 78] may well have had primary pulmonary hypertension. Indeed, angiitis was found in only one of 40 open lung biopsy specimens from patients with rheumatoid lung disease by Yousem and coworkers.[79]

Systemic Lupus Erythematosus. This connective tissue disease is characterized by inflammatory changes in connective tissue, blood vessels, and solid organs. The pleuropulmonary manifestations of this disease include pleurisy with or without effusion, atelectasis, uremic pulmonary edema, acute pneumonitis, diffuse interstitial disease, diaphragmatic dysfunction, and vasculitis.[22] Pulmonary vascular changes consisting of leukocytoclastic vasculitis and fibrinoid necrosis were found in a majority of autopsy specimens from systemic lupus erythematosus patients by Fayemi[80] and Gross and coworkers.[81] In contrast, such findings were rare in autopsy studies reported by Matthay and associates[82] and Miller and colleagues.[83] These and other investigators agree that whatever the true incidence of pulmonary vasculitis is in patients with systemic lupus erythematosus, few develop clinical manifestations of pulmonary hypertension and right heart failure.

Progressive Systemic Sclerosis. Another member of the connective tissue disease family that is also discussed in Chapter 60, progressive systemic sclerosis (scleroderma) is associated with Raynaud's phenomenon, distal vasculitis, and inflammation of the skin and internal organs. Pulmonary dysfunction is common among patients with progressive systemic sclerosis, and some degree of interstitial fibrosis is identified in almost all patients at autopsy.[22] Although severe fibrosis and, possibly, recurrent aspiration and pneumonitis may account for pulmonary hypertension and cor pulmonale in some persons, others suffer primarily from pulmonary vascular disease.[84, 85] Pulmonary vascular involvement also may predominate in patients with the CREST syndrome[86] (Fig. 54–2).

The pulmonary vascular lesions of progressive systemic sclerosis and the CREST syndrome variant are similar to vascular lesions seen in the kidneys and other organs. They consist of intimal proliferation and concentric fibrosis of the small arteries and arterioles, which frequently are narrowed or occluded. Necrotizing angiitis and fibrinoid necrosis are uncommon, indicating that the lesions lack a strong vasculitic component.[87–89] A vasoconstrictor

component similar to that seen in primary pulmonary hypertension is suggested by the frequent finding of medial hypertrophy in biopsy specimens, but plexiform changes are not encountered. Whatever its pathologic basis, the pulmonary vascular disease of progressive systemic sclerosis and the CREST syndrome should be suspected when low diffusing capacity for carbon monoxide is found by pulmonary function testing.[90]

Polymyositis and Dermatomyositis. Polymyositis is an inflammatory disease of skeletal muscle that causes weakness and atrophy; the term dermatomyositis describes a characteristic skin rash.[22] Interstitial lung disease is the most common pulmonary manifestation of these two conditions.[91] Pulmonary vascular disease has been described in two patients, both of whom on further analysis were thought to have progressive systemic sclerosis.[92] It therefore appears that vasculitis occurs infrequently, if at all.

Mixed Connective Tissue Disease. Patients with mixed connective tissue disease have clinical features characteristic of systemic lupus erythematosus, progressive systemic sclerosis, and polymyositis and dermatomyositis in addition to antibodies to extractable nuclear antigen.[93] Although lung disease has been assumed to be absent or mild in most of these patients, abnormal pulmonary function tests, including a reduced diffusing capacity for carbon monoxide, have recently been reported.[94] In addition, severe pulmonary involvement has been described by Jones and coworkers[95] and by Wiener-Kronish and associates.[96] Some autopsies performed on patients with mixed connective tissue disease revealed vasculitic changes similar to those seen in systemic lupus erythematosus and other connective tissue disorders; other examinations disclosed lesions more characteristic of primary pulmonary hypertension (Fig. 54–3) and thromboembolic disease. Thus, the nature of the pulmonary vascular involvement in patients with mixed connective tissue disease is unresolved.

Classic Polyarteritis Nodosa. As noted earlier, Kussmaul and Maier[5] in 1866 introduced the term periarteritis nodosa to describe patients with a necrotizing vasculitis of the small- and medium-sized muscular arteries that was associated with subcutaneous skin nodules. Although subsequent investigators applied this term to various vasculitides involving other blood vessels, Zeek[6, 7] limited its use to patients with the lesions that Kussmaul and Maier originally described. Rose and Spencer[97] preferred the term polyarteritis nodosa, which rightfully drew attention away from perivascular phenomena and emphasized the multiorgan involvement so characteristic of this disease. Most investigators today use polyarteritis nodosa to describe a widespread vasculitis that involves a neutrophilic inflammation of the blood vessels and perivascular space associated with intimal proliferation, fibrinoid necrosis, vessel occlusion and aneurysmal dilatation, and tissue ischemia and infarction. Although the cause is uncertain, hepatitis B infection is frequently implicated.

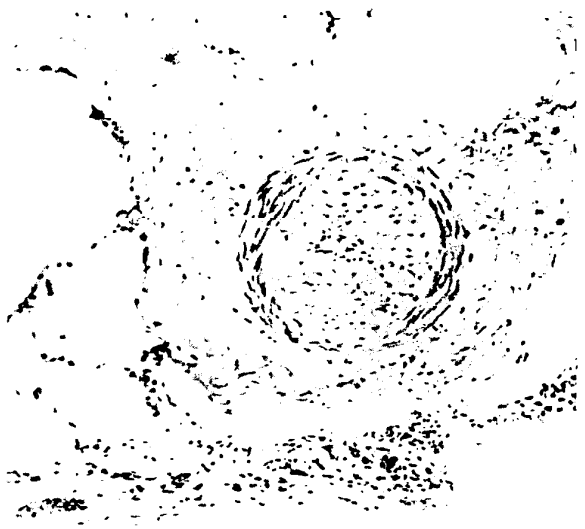

Figure 54–3. Hematoxylin and eosin stain of autopsy specimen of lung from a patient with mixed connective tissue disease. Note marked endothelial proliferation and endarteritis obliterans in a small pulmonary artery. (Courtesy of Martha L. Warnock, M.D.; reproduced with permission from Luce, J. M.: Vasculitis, primary pulmonary hypertension, and arteriovenous fistulas. *In* Murray, J. F., Nadel, J. A. [eds]: Textbook of Respiratory Medicine. Philadelphia, W. B. Saunders, 1988.)

Classic polyarteritis nodosa may occur in patients of all ages, most of whom do not have an allergic history. The clinical manifestations of this disease depend on the number of organs involved. Vasculitis frequently affects the joints, liver, abdominal viscera, and peripheral and central nervous systems.[14] Renal disease is caused by either vasculitis or glomerulonephritis. Polyarteritis nodosa also may involve the testes, epididymis, bladder, and ovaries. Coronary arteritis is especially common in younger patients. Despite the importance of subcutaneous nodules in the original description, skin involvement is far from universal in polyarteritis nodosa. In fact, the term *cutaneous periarteritis nodosa* has been introduced to describe patients with nodules, livedo reticularis, and ulcers but little evidence of systemic disease.[98]

Although polyarteritis nodosa may be distributed throughout the body, the lungs usually are spared. Sweeney and Baggenstoss[99] detected vasculitis in the bronchial and pulmonary arteries in 8 of 28 patients autopsied at the Mayo Clinic before 1950, but these patients had granulomatous lesions with eosinophilic, rather than neutrophilic, infiltration. In 1945, Wilson and Alexander[100] reported that asthma and peripheral eosinophilia were present in a large number of the 300 patients reported until then in the literature. Rose and Spencer,[97] who analyzed 104 cases from London hospitals from

1946 to 1953, found that only 14 patients with polyarteritis nodosa had lung involvement. Twelve of the 14 patients had asthma, 7 had peripheral eosinophilia, and 7 had granulomatous lesions in the lungs and other organs. In retrospect, it appears that most, if not all, of the patients once thought to have polyarteritis nodosa with pulmonary involvement actually had allergic granulomatosis and angiitis, as described by Churg and Strauss[23] in 1951.

Giant Cell (Temporal) Arteritis. The symptoms of giant cell (temporal) arteritis include headache, tenderness of the temporal arteries, myalgias, and ocular abnormalities that may progress to blindness, vertigo, dementia, and cerebrovascular accidents.[17] These symptoms occur more frequently in women than in men, usually are associated with mild anemia and elevation of the erythrocyte sedimentation rate, and should respond to low doses of corticosteroids. Biopsy of the temporal artery (or other cranial arteries at autopsy) reveals an inflammatory infiltrate consisting of lymphocytes and giant cells, intimal proliferation, and destruction of elastic membranes. Immunofluorescent studies demonstrate immunoglobulin and complement deposition in the renal walls.

Temporal arteritis traditionally has been thought of as a local process, in contrast to *polymyalgia rheumatica*, a syndrome consisting of fever, weakness, weight loss, and pain and stiffness of the proximal limb muscles and back. Yet many patients with temporal arteritis also have symptoms of polymyalgia rheumatica; patients with polymyalgia rheumatica may develop temporal arteritis; and temporal artery biopsies in patients with polymyalgia rheumatica have revealed vasculitic changes. Most important, involvement of extracranial vessels, including the aorta and pulmonary arteries,[101, 102] has been reported in patients with temporal arteritis. These findings suggest that the underlying disorder in both temporal arteritis and polymyalgia rheumatica is a generalized vasculitis.[83]

Takayasu's Disease. In 1908 Takayasu[103] described a young woman with cataracts and arteriovenous anastomoses around the optic discs who subsequently was shown to lack pulses in her arms. Later investigators determined that the "pulseless disease" resulted from a granulomatous vasculitis involving primarily the aorta and its branches and that these lesions led to blood vessel narrowing and occlusion with aneurysm formation. These histologic changes have been reported predominantly in young Japanese women and are associated with an elevated erythrocyte sedimentation rate. Despite therapy with corticosteroids and anticoagulants, Takayasu's disease may cause blindness, cerebrovascular accidents, severe hypertension, left ventricular failure, and aortic aneurysm rupture.[19, 104] Pulmonary symptoms have been reported in patients with this disorder. Pulmonary artery involvement, with or without pulmonary hypertension, has been confirmed by angiographic and autopsy studies, and pulmonary arteritis probably occurs in the majority of patients.[19, 106–108]

Behçet's Syndrome. Behçet's syndrome was described in 1937 as a symptom complex of recurrent aphthous stomatitis, genital ulceration, and uveitis.[109] It subsequently has become recognized as a systemic disorder that also may involve the gastrointestinal tract, cardiovascular system, brain, kidneys, and lungs.[110] The underlying pathologic process is a vasculitis involving neutrophils and mononuclear cells that usually affects veins, venules, and capillaries. Immunoglobulin staining of the lesions has revealed immunoglobulin G and complement.

Pulmonary involvement occurs in approximately 10% of patients with Behçet's syndrome and includes recurrent pneumonia and often fatal episodes of hemoptysis.[111–113] The latter problem has been attributed in the past to vasculitis of small lung vessels and to rupture of bronchial veins when intraluminal pressure is increased by thrombosis of the superior cava.[114] However, hemoptysis also may result from rupture of large pulmonary artery aneurysms and arteriovenous fistulas.[113, 115]

Hughes-Stovin Syndrome. Hughes and Stovin[116] in 1959 described two patients who died from massive hemoptysis due to rupture of segmented pulmonary artery aneurysms. Recurrent venous thrombosis also was detected in these patients, as was intracranial hypertension that probably was related to thrombosis of intracranial and extracranial vessels. That these abnormalities were caused by vasculitis was suggested by the finding of an inflammatory infiltrate consisting largely of lymphocytes and plasma cells in the walls of the elastic pulmonary arteries at autopsy. Neither these patients nor similar patients subsequently reported by Durieux and associates[115] and Meireles and coworkers[117] met the diagnostic criteria for Behçet's syndrome. The Hughes-Stovin syndrome therefore appears to be either a separate entity or a variant of Behçet's syndrome.

Eosinophilia-Myalgia Syndrome. An epidemic of the eosinophilia-myalgia syndrome in the late 1980s has been linked to the dietary ingestion of contaminated L-tryptophan, with over 1,500 cases reported to the Centers for Disease Control through 1990.[25, 118–121] This compound was widely used as an over-the-counter remedy for insomnia, stress, and depression. Although the pathogenesis remains unclear, the disease appears to result from a reaction to a contaminant that was introduced during the manufacturing process.[122, 123] The clinical manifestations of eosinophilia-myalgia syndrome include myalgias, arthralgias, skin rashes, muscle pain, edema, fatigue, neuropathy, and marked peripheral eosinophilia.[124] Over half of patients with eosinophilia-myalgia syndrome have respiratory complaints, with dyspnea occurring most frequently.

Acute eosinophilic pneumonitis, pleural effusions, chronic interstitial lung disease, and chronic pulmonary hypertension have been reported.[125-127] Lung biopsies have demonstrated the presence of vasculitis with fibrointimal hyperplasia, often associated with varying degrees of interstitial infiltrate.[126, 127] Although some patients have improved with the discontinuation of L-tryptophan or corticosteriod therapy, the response is often incomplete and the disease may be chronic and progressive.[124]

PRIMARY PULMONARY HYPERTENSION

Primary pulmonary hypertension is a disease in which there is a persistent elevation of pulmonary artery pressure without demonstrable cause.[128] Although there is no uniformly accepted hemodynamic definition for pulmonary hypertension, the primary pulmonary hypertension registry of the United States National Institute of Health[128] and the Japanese Primary Pulmonary Hypertension Research Committee[129] require a resting mean pulmonary artery pressure greater than 25 mm Hg or a mean pressure in excess of 30 mm Hg during exercise. These criteria facilitate the inclusion of patients identified early in the course of their illness.

Classification

Primary pulmonary hypertension by definition is a diagnosis of exclusion. It must be differentiated on clinical grounds from pulmonary hypertension related to chronic pulmonary thromboembolism, chronic airflow obstruction, parenchymal lung disease, severe hypoventilation, left ventricular failure, left-sided valvular heart disease, and congenital heart disease with intracardiac shunts.[128] A World Health Organization[130] conference in 1973 categorized chronic pulmonary thromboembolism, pulmonary veno-occlusive disease, and plexogenic pulmonary arteriopathy under the rubric pulmonary hypertension of unknown cause. However, the morphologic characteristics of these conditions are quite distinct despite their clinical similarities, and plexogenic pulmonary arteriopathy is the histologic lesion that most investigators associate with primary pulmonary hypertension.[131] Pulmonary veno-occlusive disease most likely represents a variant of plexogenic pulmonary arteriopathy.

Epidemiology

Primary pulmonary hypertension was first described at autopsy by Romberg[132] in 1891. Patients with pulmonary hypertension of unknown cause were reported infrequently over the next 60 years, only 2 cases being identified from 10,000 consecutive autopsies at Massachusetts General Hospital.[133] However, the condition was recognized more commonly after the advent of cardiac catheterization. Wood[134] in 1950 detected 6 cases of what he called idiopathic pulmonary hypertension among 233 unselected British patients with presumed congenital heart disease, 152 of whom were catheterized. One year later, the term primary pulmonary hypertension was introduced by Dresdale and associates[135] in a detailed clinical and hemodynamic study of similar patients.

Since these original studies, primary pulmonary hypertension has been reported with increased frequency. Shephard and colleagues[136] and Chapman and coworkers[137] described 14 patients with the condition in 1957; in 1958, Yu[138] reviewed the findings in 55 persons over age 12 reported previously in the literature. Wolcott and colleagues[139] selected 23 cases from among Mayo Clinic patients seen in the 20-year period from 1946 to 1965. A review of 17,901 autopsies performed on persons older than 1 year of age from 1944 to 1981 at the Johns Hopkins Hospital yielded 24 cases of primary pulmonary hypertension; this amounted to a prevalence of 0.13% of all patients.[140] The primary pulmonary hypertension registry included 187 cases collected from 32 centers between 1981 and 1985. In 1984, Rich and Brundage[141] noted that primary pulmonary hypertension was found at autopsy in approximately 1% of patients with cor pulmonale.

Primary pulmonary hypertension customarily has been considered a disease of young women. Indeed, all of Wood's[134] 6 patients were women between 20 and 45 years of age, as were the 3 patients described by Dresdale and associates.[135] An overall female-to-male ratio of 1.7:1 was found in the United States registry.[128] However, primary pulmonary hypertension has been reported in both sexes within a wide age range. For example, the mean age of patients in the registry series[128] was 36 years, with a range of 1 to 81 years, whereas the mean age of Japanese patients was 31 years with a range of 11 to 66 years.[129] The disease appears to affect older men and women in equal numbers, although the majority of younger patients continue to be female.[141]

Pathology

Wood[142] in 1958 divided pulmonary hypertension into six types: *passive*, as seen with increased pulmonary venous pressure due to raised left atrial or ventricular pressure; *hyperkinetic*, caused by increased pulmonary blood flow; *obstructive*, resulting from pulmonary embolism or thrombosis; *obliterative*, manifested by a reduction of pulmonary vascular capacity; *vasoconstrictive*, brought about by

functional and presumably reversible vasospasm; and *polygenic*, arising in two or more of the preceding ways (further details are provided in Table 52–3). Vasoconstrictive pulmonary hypertension occurred most characteristically in response to alveolar hypoxia and usually responded to the inhalation of oxygen or the injection of acetylcholine into the pulmonary artery. Reversible vasoconstriction also was seen as an added component of the passive hypertension of mitral stenosis and the hyperkinetic hypertension caused by congenital left-to-right intracardiac shunts before the onset of Eisenmenger's syndrome. The histologic lesions observed in these reversible kinds of pulmonary hypertension consisted of medial hypertrophy of the pulmonary artery and scant intimal hyperplasia.

Also in 1958, Heath and Edwards[143] documented the pathology of hypertensive pulmonary vascular disease in a study of 67 patients with congenital heart disease and 2 patients with primary pulmonary hypertension. These investigators argued that the progression of lesions in these patients was so stereotyped as to allow division of the structural effects of pulmonary hypertension into six grades as follows: grade 1, medial hypertrophy of the pulmonary arteries and arterioles without intimal changes; grade 2, medial hypertrophy with cellular intimal proliferation; grade 3, medial hypertrophy, intimal proliferation, and intimal fibrosis; grade 4, progressive generalized vascular dilation and occlusion by intimal fibrosis and fibroelastosis; grade 5, appearance of dilation lesions, including vein-like branches of occluded pulmonary arteries, plexiform lesions, angiomatoid lesions, and cavernous lesions; and grade 6, necrotizing arteritis.

The Heath and Edwards' grading system focused on the muscular pulmonary arteries 100 to 1,000 μm in size. Grades 1 and 2, which were characterized by medial thickening, were comparable to the reversible vasoconstrictive phase of Wood's scheme. In grades 3 and 4, intimal changes led to progressive obstruction of the vessels, which then dilated in the presence of high pressure. Some of the dilated areas evolved into microaneurysms in which there was endothelial proliferation and the formation of in situ thrombosis; these made up the characteristic plexiform lesions. In grade 5, the dilation became rigid, and hemosiderin was

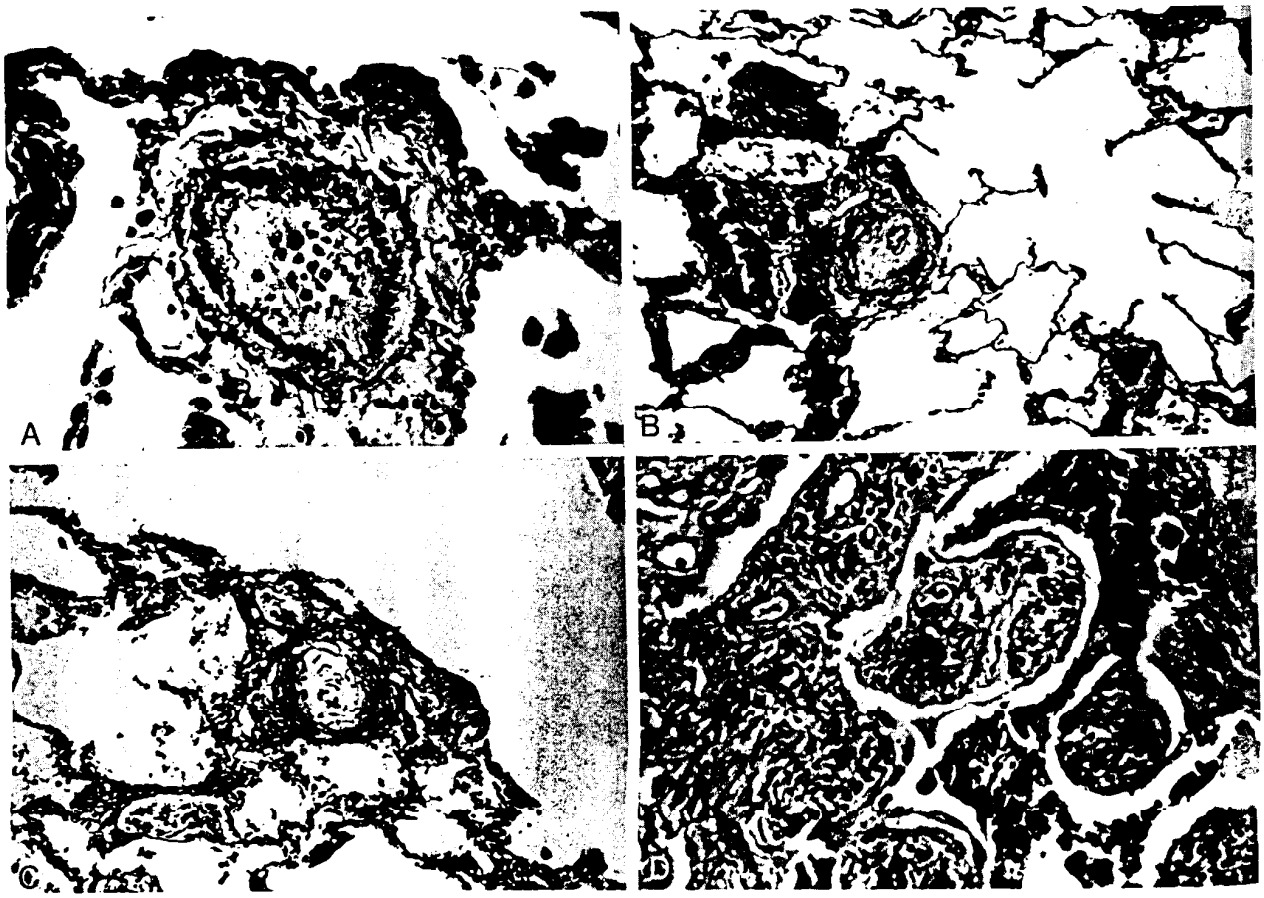

Figure 54–4. Pathologic changes of primary pulmonary hypertension. *A*, Elastic stain demonstrating medial hypertrophy and intimal proliferation. *B*, Hematoxylin and eosin stain demonstrating eccentric intimal fibrosis. *C*, Hematoxylin and eosin stain demonstrating concentric intimal fibrosis (onionskinning). *D*, Hematoxylin and eosin stain demonstrating a plexiform lesion.

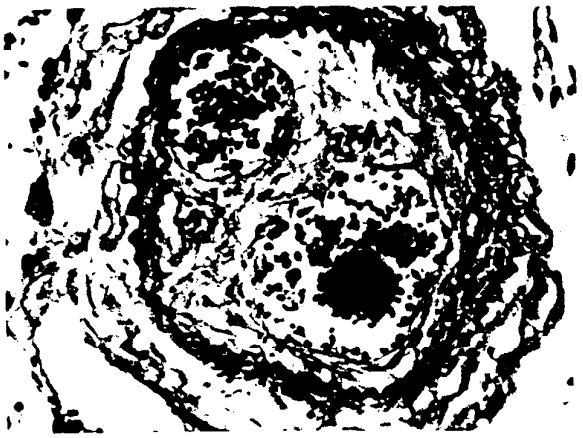

Figure 54–5. Elastic stain of lung tissue from patient with chronic pulmonary thromboembolism showing that there is little medial hypertrophy and that the organized thrombus has recanalized.

truded from vessels that either burst or allowed the diapedesis of erythrocytes. Grade 6 was seen rarely and involved perivascular neutrophilic inflammation and fibrinoid necrosis.

Heath and Edwards[143] lumped the pathology of congenital heart disease and primary pulmonary hypertension together, and a large series of patients with the latter disorder was not available until 1970. In that year, Wagenvoort and Wagenvoort[144] described the morphology of the pulmonary vessels of 150 persons in whom the diagnosis of primary pulmonary hypertension had been made on clinical grounds. Despite their common diagnosis, the cases could be divided into several groups on histologic analysis: chronic pulmonary thromboembolism, chronic pulmonary venous hypertension, pulmonary veno-occlusive disease, sarcoidosis, chronic bronchitis and pulmonary emphysema, pulmonary schistosomiasis, and vasoconstrictive primary pulmonary hypertension. The patients with the last disorder were the largest group, consisting of 36 men and 74 women with a mean age of 23 years and an age range of from 4 days to 69 years.

The lesions that Wagenvoort and Wagenvoort attributed to vasoconstrictive primary pulmonary hypertension were strikingly similar to those described earlier by Heath and Edwards[143] and Wood.[142] The earliest abnormalities were medial hypertrophy of the muscular pulmonary arteries and muscularization of the arterioles. These findings were especially prominent in children and were the only irregularities found in young infants. Although the medial thickening might be interpreted as a persistence of the high-resistance fetal circulation, it was considerably greater than that observed in infants of the same age. Less marked in children but apparent in all adults studied were intimal proliferation and laminar intimal fibrosis that gave an onionskin appearance to the pulmonary arteries. This pattern was not seen in any patients with initially unsuspected chronic pulmonary thromboembolism and also was absent from an additional 20 patients with known thromboembolic disease.

Dilation lesions, including the plexiform variety, were observed in 77 patients with vasoconstrictive primary pulmonary hypertension and one patient with schistosomiasis (who also had *Schistosoma mansoni* ova) but was not evident in persons with chronic pulmonary thromboembolism or other disorders. Necrotizing arteritis occurred in 34 patients with chronic pulmonary thromboembolism; it never involved the veins as it does in pulmonary veno-occlusive disease. Wagenvoort and Wagenvoort[144] noted that vasculitis occurred only in persons with advanced disease and probably was a result rather than a cause of pulmonary hypertension, in contrast to the true pulmonary vasculitides. They believed that the progression of lesions in primary pulmonary hypertension was entirely consistent with a vasoconstrictive mechanism.

Subsequent investigators[131] confirmed the findings of Wagenvoort and Wagenvoort,[144] including the histologic distinctions between primary pulmonary hypertension (Fig. 54–4), chronic pulmonary thromboembolism (Fig. 54–5), and pulmonary veno-occlusive disease (Fig. 54–6). Nevertheless, the vasoconstrictive nature of primary pulmonary hypertension has not been universally accepted; Anderson and coworkers,[145] for example, concluded from their autopsy experience that the essential lesion in this disorder is not medial hypertrophy but intimal proliferation of the pulmonary arteries. Because the pathogenesis of primary pulmonary

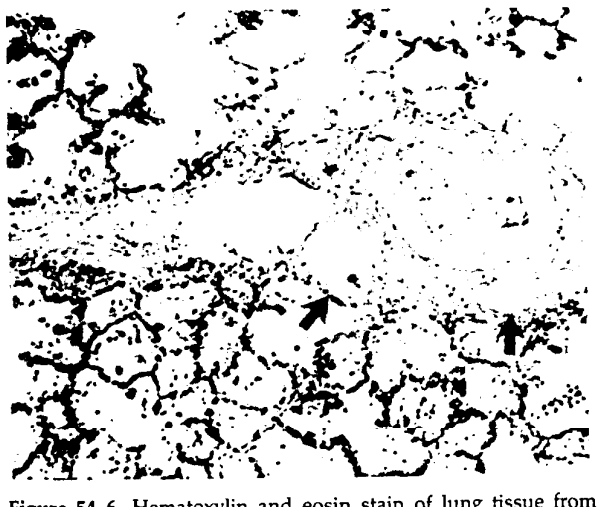

Figure 54–6. Hematoxylin and eosin stain of lung tissue from patient with pulmonary veno-occlusive disease showing occluded vein and dilated perivenous lymphatics (arrows). (Courtesy of Martha L. Warnock, M.D.; reproduced with permission from Luce, J. M.: Vasculitis, primary pulmonary hypertension, and arteriovenous fistulas. *In* Murray, J. F., Nadel, J. A. [eds.]: Textbook of Respiratory Medicine. Philadelphia, W. B. Saunders, 1988.)

hypertension is still open to debate, the term *vasoconstrictive primary pulmonary hypertension* has been superseded by the term *plexogenic pulmonary arteriopathy*,[131] despite the fact that plexiform lesions also may be seen in patients with congenital heart disease and pulmonary schistosomiasis.[144]

Pathogenesis and Etiology

Although the pathogenesis of primary pulmonary hypertension is uncertain, the pathologic similarity between this disease and congenital intracardiac shunts strongly suggests an early vasoreactive phase. Functional vasoconstriction also is supported by the demonstration of immediate reductions in the pulmonary artery pressure of some patients during cardiac catheterization and reports of long-term sustained hemodynamic responses to therapy and spontaneous regression in a few patients, including an 11-year-old girl.[146] Presumably, such persons have a preponderance of medial hypertrophy rather than intimal proliferation and fibrosis. Whether their lesions are chronologically earlier than or pathogenetically different from those of patients with less reversible primary pulmonary hypertension is unclear.

The cause of vasconstriction in primary pulmonary hypertension also has not been characterized; endothelin-1 has been proposed as a possible mediator.[146a] Goodale and Thomas,[133] among others, argued that disease was due to persistence of the vasoreactive fetal circulation, but their argument was contradicted by the findings of Wagenvoort and Wagenvoort,[144] cited earlier. Dresdale and coworkers,[135] who named the condition, speculated that patients with primary pulmonary hypertension might be congenitally sensitive to sympathetic stimulation. Although its mechanism has not been elucidated, such sensitivity is supported by reports of primary pulmonary hypertension in identical twins,[147] two siblings and their father,[148] five members of one family across three generations,[149] and six members of the same family over two generations.[150] Review of some of these families suggests that the gene for pulmonary hypertension is transmitted in an autosomal-dominant pattern. Familial disease was reported in 7% of patients in the United States registry.[128] Susceptibility to high-altitude pulmonary hypertension appears to have a genetic basis in animals[151] and humans,[152] and wide individual and species variation in vascular reactivity is well described.

The association of primary pulmonary hypertension and Raynaud's phenomenon[153–155] also supports the notion of a vasoconstrictive pathogenesis. Raynaud's phenomenon was either the initial complaint or an eventual symptom in 30% of patients with primary pulmonary hypertension seen at the Mayo Clinic,[139] and in 10% of patients in the United States registry.[128] Primary pulmonary hypertension has been linked with Raynaud's phenomenon, migraine, and variant angina as manifestations of a generalized vasospastic disorder.[156]

Raynaud's phenomenon also is common among patients with collagen vascular disorders. The concurrence of these two abnormalities and primary pulmonary hypertension was first noted in 1960 by Rawson and Woske,[157] who hypothesized that primary pulmonary hypertension might actually be a collagen vascular disease. Since that time, antinuclear antibodies have been detected in the sera of up to 30% of persons with primary pulmonary hypertension,[128, 158] and pulmonary hypertension has been described in an even larger number of persons with rheumatoid arthritis,[76–78] systemic lupus erythematosus,[80–83] progressive systemic sclerosis and the CREST syndrome,[84–89] polymyositis and dermatomyositis,[91, 92] and mixed connective tissue disease.[94–96]

Some patients with these diseases have been found at autopsy to have plexogenic pulmonary arteriopathy. Furthermore, medial hypertrophy and concentric intimal fibrosis are prominent in progressive systemic sclerosis, although plexiform lesions are not seen. The frequent finding of Raynaud's phenomenon and the occasional response to vasodilators in patients with progressive systemic sclerosis and pulmonary hypertension prompted Sackner and associates[84] to suggest the likely role of generalized vasospasm in progressive systemic sclerosis.

Raynaud's phenomenon, progressive systemic sclerosis, and primary pulmonary hypertension occur most commonly among women. Primary pulmonary hypertension also may be noted initially during pregnancy,[159, 160] when pulmonary vascular reactivity normally is blunted and pulmonary artery pressure should be low.[161] In addition, primary pulmonary hypertension has been reported with striking frequency in patients taking oral contraceptives.[162, 163] These observations suggest that estrogens and perhaps other vasoactive hormones play a role in primary pulmonary hypertension, although this role has never been well characterized. In their early series, Shepherd and associates[136] surmised that primary pulmonary hypertension might be caused by nonfatal amniotic fluid embolism. Yet signs of such embolism were not detected at autopsy in the two female patients in this series, and four other women with primary pulmonary hypertension had not been pregnant according to their histories.

Portal hypertension is another disease occasionally associated with pulmonary hypertension, although the expected structural alteration in the pulmonary vessels is diffuse dilation of the arteries and veins.[164] Mantz and Craige[165] first described the simultaneous occurrence of portal and pulmonary hypertension in a patient with portal vein throm-

bosis and speculated that multiple emboli emanating from portacaval anastomosis were responsible for the pulmonary hypertension. Naeye[166] in 1960 reported six cases of coexisting portal and pulmonary hypertension and also implicated embolization from the portal vein. It has also been suggested that a vasoactive agent or a substance harmful to the pulmonary circulation might have been produced in the gut but escaped hepatic detoxifying mechanisms. This hypothesis is supported by reports of six patients who had been treated by portal-systemic shunting before the clinical onset of pulmonary hypertension[167, 168] and patients with plexogenic arteriopathy associated with congenital agenesis of the portal vein.[169]

The possibility that the liver is not metabolizing a toxin or vasoconstrictive substance in patients with portal and pulmonary hypertension is strengthened by mounting evidence of dietary pulmonary hypertension.[170] In 1957, Bras and colleagues[171] described veno-occlusive disease of the liver in Jamaican patients who drank bush tea made from *Crotalaria spectabilis,* a plant containing the pyrrolidine alkaloid monocrotaline. Another alkaloid, fulvine, causes similar disease following the ingestion of *Crotalaria fulva.* Although these agents are hepatotoxic in humans, they do not produce pulmonary lesions. However, both monocrotaline and fulvine damage the pulmonary vessels in rats.[172, 173] Neither laminar intimal fibrosis nor plexiform lesions are part of the pulmonary toxicity of these agents, but these reports serve as reminders of the fact that substances taken by mouth can cause pulmonary vascular disease.

This possibility was vividly dramatized between 1967 and 1970 in Switzerland, Austria, and Germany, where a 20-fold increase in pulmonary hypertension was observed after the introduction of aminorex, an appetite suppressant resembling epinephrine and amphetamine.[174] The pulmonary lesions produced by this agent resembled plexogenic pulmonary arteriopathy in every respect. Although the case against aminorex was weakened by the facts that 20% of patients with idiopathic pulmonary hypertension in Central Europe did not take the drug, only one in a thousand persons taking the drug actually developed pulmonary hypertension, and an animal model could not be created,[175] the case was strengthened by the observation that the incidence of pulmonary hypertension decreased to its previous level after aminorex was withdrawn from the market. Pulmonary hypertension has been associated with another appetite suppressant with similar chemical structure, fenfluramine,[176] and reversible pulmonary hypertension has been reported after discontinuation of a similar agent.[177]

Pulmonary hypertension also has been reported in patients receiving phenformin, a biquanide bearing little resemblance to the catecholamines.[178] In 1983, an epidemic of pulmonary hypertension was observed in Spain among people who ingested rapeseed oil contaminated with aniline and acetanilide dyes used to mark the oil as unfit for human consumption.[179] Most of the poisoned patients with pulmonary complications died of increased permeability pulmonary edema shortly after ingestion. However, several survivors manifested pulmonary hypertension during cardiac catheterization, and pathologic studies revealed medial thickening and intimal proliferation, early histologic findings of plexogenic pulmonary arteriopathy.[180] Strikingly similar findings have been observed in some patients who developed the eosinophilia-myalgia syndrome after the ingestion of contaminated L-tryptophan. Although the systemic manifestations predominated in most patients, several patients developed varying degrees of pulmonary hypertension, characterized by intimal proliferation and medial hypertrophy of small pulmonary arteries, in the absence of significant parenchymal lung disease.

Illicit drug use has been observed with increasing frequency as a cause of severe pulmonary hypertension; this may be due to a combination of factors, including granulomatous pulmonary arteritis resulting from a reaction to talc, which is commonly used as an adulterant of parenteral drugs, obstruction of the vasculature due to other foreign material such as cotton fibers, and the vasoconstrictive properties of some agents, such as cocaine.

Symptoms

Dyspnea is the cardinal symptom of primary pulmonary hypertension, occurring in more than 95% of patients in the major clinical series.[128, 129, 135–139] Breathlessness is the presenting symptom in 60% of patients and usually is noted first on exertion, but eventually occurs at rest. Its mechanism is probably complex: the most likely cause for the dyspnea of pulmonary hypertension is the inadequacy of cardiac output relative to metabolic requirements.[181] Reeves and Grover[182] have postulated that stretch receptors on the main pulmonary arteries may also be involved. Regardless of its mechanism, Packer[183] stresses that the severity of dyspnea does not correlate with the elevation of pulmonary artery pressure in patients with primary pulmonary hypertension.

Closely related to dyspnea are sensations of fatigue and weakness, reported by a majority of patients with primary pulmonary hypertension.[128] These sensations usually are experienced before the general disability that is present with advanced disease. They presumably reflect impaired tissue oxygenation due to the depressed cardiac output in patients with primary pulmonary hypertension. This impairment may be detected during cardiac

catheterization as both a low cardiac output and a decreased mixed venous P_{O_2}.

Substernal chest pain also is commonly reported in patients with primary pulmonary hypertension.[135, 136] It frequently occurs on exertion, radiates to the left shoulder or axilla, and is relieved by rest. The pain has been likened to angina pectoris and has been attributed to coronary insufficiency in the presence of increased right ventricular work and hypoxemia;[181] this concept is supported by the occasional relief produced by nitroglycerin. However, pain may be present in young patients without coronary artery disease, prompting Viar and Harrison[184] to argue that the pain is due to distention of the pulmonary artery, whose afferents enter the nervous system along the same pathways as afferents from the heart. Another plausible but unproved explanation is that the chest pain of primary pulmonary hypertension is variant angina in patients with generalized vasospastic disease.

Syncope occurs in some patients with primary pulmonary hypertension and may be its initial manifestation.[128] This symptom also is experienced first on exertion but may happen later at rest. The syncope probably is caused by a decrease in cerebral blood flow that follows an increase in pulmonary artery pressure and a fall in cardiac output. Dresdale and associates[135] speculated that cardiac output would be especially depressed in patients with concurrent coronary insufficiency and right ventricular failure. On the other hand, James[185] believed that depression of the cardiac output results primarily from bradycardia due to ischemia of the sinus node.

Another symptom associated with primary pulmonary hypertension is hemoptysis that presumably stems from microvascular aneurysms that rupture under the high pulmonary artery pressure. In addition, hoarseness may result from pressure of the enlarged main pulmonary artery on the recurrent laryngeal nerve.[186] Peripheral edema and ascites may develop after the onset of right ventricular failure.[138]

Physical Findings

Patients with early primary pulmonary hypertension may manifest no physical abnormalities. However, signs of pulmonary hypertension and a decreased cardiac output should be evident with advanced disease. As Wood[187] observed, the hands and feet of a patient with severe pulmonary hypertension are cold, the peripheral pulse is diminished, the blood pressure is likely to be low, and the pulse pressure is reduced. Signs of systemic venous hypertension should be present, including a prominent jugular venous *a* wave, which is exaggerated by abdominal compression (hepatojugular reflux) and transmitted to the liver in a presystolic hepatic pulse, and prominent *c-v* waves, which are indicative of tricuspid regurgitation. Palpation of the chest should reveal a right ventricular lift at the left sternal border that is sustained throughout the pressure-overloaded cardiac contraction, in contrast to the unsustained parasternal impulse felt in pure volume overload.

On auscultation of the chest, the second heart sound is closely split, and the second (pulmonic) component is accentuated. The valvular closure sound should increase in intensity on inspiration and may become palpable as pulmonary artery pressure rises. A systolic ejection click reflecting sudden distention of the right ventricular wall also may be heard. A murmur of tricuspid regurgitation, heard best along the left sternal border and increasing in intensity with inspiration, is heard frequently. A pulmonary regurgitant murmur may become evident following dilation of the main pulmonary artery and its valve annulus. Diastolic vibration of the aortic valve leaflet (Graham Steell's murmur) may be present along with third and fourth heart sounds. In addition to these findings, patients with right-sided heart failure usually have peripheral edema and abdominal distention due to ascites. If tricuspid regurgitation is present, the liver may become pulsatile.

Cyanosis occurs with variable frequency in patients with primary pulmonary hypertension and is likely to be a late phenomenon.[97] It is most marked after exercise but also may be present at rest. Peripheral vasoconstriction and impaired oxygenation of arterial blood due to mixed venous hypoxemia resulting from the decreased cardiac output appear to be the most common mechanisms. Patients in whom right atrial pressure equals or exceeds left atrial pressure may develop severe hypoxemia and cyanosis owing to opening of the foramen ovale with subsequent right-to-left shunting. In addition to cyanosis, vascular plethora may be observed in hypoxemic patients with secondary polycythemia. With the exception of patients with cirrhosis and pulmonary hypertension, clubbing is not a usual manifestation of primary pulmonary hypertension. The presence of clubbing warrants a careful search for other causes of pulmonary vascular disease.

Diagnosis

Although pulmonary hypertension may be appreciated on physical examination, primary pulmonary hypertension cannot be distinguished from the other causes of pulmonary hypertension by examination alone. The major entities in the differential diagnosis are chronic pulmonary thromboembolism (Chapter 53); cardiac disorders such as congenital heart disease, mitral stenosis, and left atrial tumors (Chapter 88); and pulmonary veno-

occlusive disease (discussed subsequently). Although the severity of pulmonary hypertension may be assessed by examination, laboratory evaluation is required for precise quantitation, as stressed also in Chapter 31.

Blood studies are an important part of the laboratory evaluation. The complete blood count is particularly helpful in documenting polycythemia, which is present in hypoxemic patients with primary pulmonary hypertension.[128] An even smaller number are anemic, thrombocytopenic, or both. Two patients recently have been reported with microangiopathic hemolytic anemia and primary pulmonary hypertension, one of whom had portal hypertension as well. In both cases, intravascular fragmentation of erythrocytes and platelets was attributed to blood flow through plexiform lesions in the pulmonary circulation.[188, 189] Pulmonary hypertension has also been associated with a familial platelet storage pool disease, in which platelet function was impaired and plasma levels of serotonin were elevated.[190]

The plain chest roentgenogram is potentially useful in suggesting the presence of pulmonary hypertension and in providing clues of underlying conditions such as parenchymal lung disease (Fig. 54–7). In patients with primary pulmonary hypertension, the roentgenogram characteristically reveals protrusion of the main pulmonary artery, increased width of the descending branch of the right pulmonary artery, peripheral oligemia, and an increase in the cardiothoracic ratio.[187] Analysis of the chest roentgenograms of 59 patients from the Japanese Primary Pulmonary Hypertension Research Committee[191] demonstrated a positive correlation between the cardiothoracic ratio and right atrial pressure. The increased ratio did not correlate with pulmonary artery pressure, however, suggesting that it is caused mainly by right heart failure.

Figure 54–7. Chest roentgenogram from a patient with primary pulmonary hypertension showing the marked dilation of the main pulmonary arteries and right ventricular enlargement.

Systemic arterial blood gas analysis in patients with primary pulmonary hypertension usually reveals a low P_{CO_2} and a normal pH, reflecting chronic respiratory alkalosis. The systemic arterial P_{O_2} may be normal or abnormal, but the alveolar-to-arterial P_{O_2} difference usually is increased.[128] Several mechanisms have been proposed for the hypoxemia of patients with primary pulmonary hypertension, including diffusion impairment caused by a reduction in the number of pulmonary vessels coupled with the shortened time spent by erythrocytes in traversing the pulmonary circulation; ventilation-perfusion mismatching due to alterations in pulmonary blood flow and concomitant conditions such as bronchospasm; and right-to-left intracardiac shunting through a patent foramen ovale.[30] Dantzker and Bower[192] demonstrated with the multiple inert gas elimination technique that the hypoxemia is due to a combination of ventilation-perfusion mismatching, intrapulmonary shunt, and a low mixed venous P_{O_2} resulting from a reduced cardiac output.

Pulmonary function tests performed in patients with primary pulmonary hypertension usually reveal normal expiratory flow rates with normal or mildly reduced lung volumes.[128] The modest restrictive defect has been attributed to diminished distensibility of the pulmonary vessels.[193] The diffusing capacity for carbon monoxide is often reduced to a mild or moderate degree.[128]

Exercise testing serves to bring out physiologic abnormalities in patients with primary pulmonary hypertension if these abnormalities are not present at rest. Characteristically, patients with pulmonary hypertension will achieve their target heart rate and anaerobic threshold at low levels of exercise, often accompanied by a reduction in the systemic arterial P_{O_2} or an increase in the alveolar-to-arterial P_{O_2} difference. The dead space to tidal volume ratio either fails to decrease as it should in normal persons or actually increases during graded exercise.[30] Of course, exercise may be accompanied by an increase in pulmonary artery pressure and a demand for oxygen transport that cannot be met by a compromised circulation. Exercise testing, therefore, may be hazardous in patients with primary pulmonary hypertension, and a death has been reported during one such study.[153]

The electrocardiogram usually discloses right ventricular hypertrophy in patients with advanced primary pulmonary hypertension.[187] Electrocardiographic criteria for right ventricular hypertrophy include a QRS axis in the frontal plane that is greater than or equal to 110 degrees, an R wave in lead V_1 that is greater than 5 mm, an R-to-S ratio in V_1 that is greater than 1, and an R-to-S ratio in lead V_6 that is less than 1. Patients also may manifest right atrial

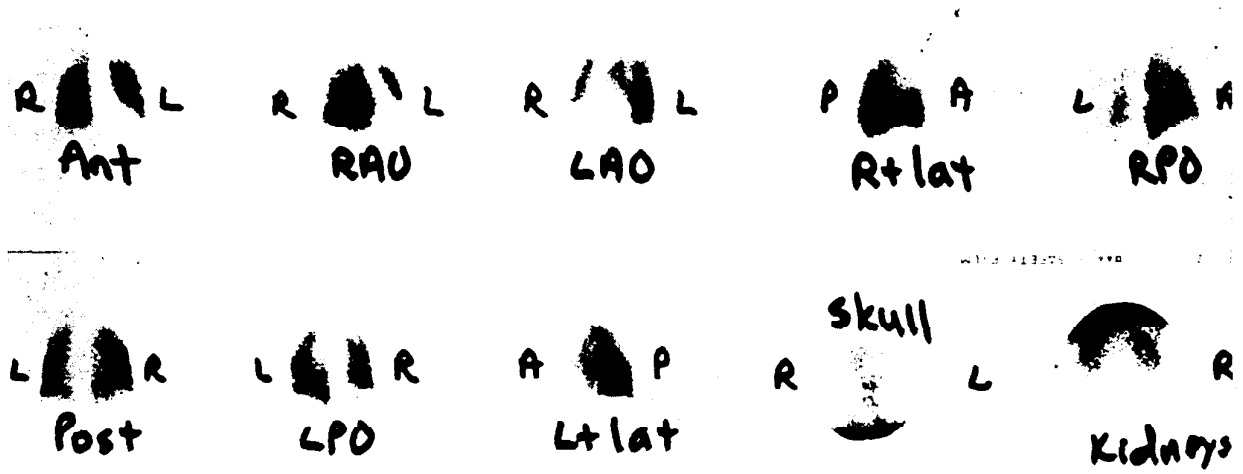

Figure 54–8. Perfusion lung scan from a patient with primary pulmonary hypertension with a right-to-left shunt through a patent foramen ovale. The overall pattern of perfusion is normal; the presence of a shunt is demonstrated by the appearance of tracer when scanning over the skull and kidneys. Projections are as follows: Ant = anterior, LAO = left anterior oblique, L + lat = left lateral, LPO = left posterior oblique, Post = posterior, RAO = right anterior oblique, R + lat = right lateral, RPO = right posterior oblique.

enlargement with a symmetric and peaked P wave in lead II that is greater than 2.5 mm in amplitude. ST segment depression and T wave inversion may be seen in the anterior chest leads. These abnormalities may not be present if pulmonary hypertension is not pronounced or if patients are young.[181]

The echocardiogram may be helpful in documenting pulmonary hypertension and in ruling out conditions such as mitral stenosis and left ventricular dysfunction. Primary pulmonary hypertension has been associated in one-dimensional echocardiography with midsystolic notching, diminution of the *a* dip, prolongation of the right ventricular preejection period, increased right ventricular systolic dimensions, and midsystolic fluttering of the pulmonary valve.[194–196] Two-dimensional echocardiography helps quantitate right atrial and right ventricular size and may identify systolic flattening or diastolic bulging of the interventricular septum due to increased pulmonary artery pressure.[197] Intracardiac shunting may be observed after the intravenous injection of microbubbles. In addition, Doppler techniques may allow estimation of pulmonary artery pressure.[198, 199]

Perfusion lung scanning has been used primarily to differentiate primary pulmonary hypertension from chronic pulmonary thromboembolism. Wilson and coworkers[200] scanned 21 patients with chronic obliterative pulmonary hypertension and observed three patterns: large multiple, segmental defects; multiple ill-defined defects; and no defects. The first pattern occurred exclusively among patients with documented thromboembolic disorders, whereas the third pattern was found exclusively among patients with primary pulmonary hypertension. The second pattern was attributed to disease of the small pulmonary arteries, although recurrent embolization or idiopathic hypertension could not be excluded. *D'Alonzo and associates*[201] studied 25 patients; all 8 patients with chronic pulmonary thromboembolism had lung scans with a high probability of embolic disease due to multiple segmental defects, whereas 17 patients with primary pulmonary hypertension had scans that were normal or had a low probability of embolism. This study suggests that lung scans are highly specific in differentiating the two conditions and might replace angiography, especially because of their relative safety. Not all investigators agree with this suggestion, however, and perfusion scanning was associated with sudden death in a patient with obliterative pulmonary vascular disease,[202] presumably due to transient obstruction of a critical number of small pulmonary vessels by the macroaggregates of radiolabeled albumin. Nevertheless, perfusion scanning is generally considered to be a safe procedure in patients with unexplained pulmonary hypertension; reduced doses of tracer material can be used for scanning if concern exists about patient safety. Scanning over the head or abdomen may yield images of the brain or kidneys, indicative of a right-to-left shunt (Figure 54–8).

As indicated in the preceding discussion, pulmonary angiography remains the most accepted method of ruling out chronic pulmonary thromboembolism and other disorders in patients suspected of having primary pulmonary hypertension (Fig. 54–9).[97] Arteriography is practical in that it can be combined with pressure measurements in one session. However, death has been reported in patients with pulmonary hypertension undergoing arteriography, particularly when overt right ventricular failure is present.[203] The risk of compromising the pulmonary vascular bed during arteriography may

Figure 54-9. Left pulmonary angiogram from a patient with primary pulmonary hypertension showing the characteristic "pruning" of the peripheral vessels.

be decreased by using smaller amounts of nonionic contrast material with selective injections or by digital subtraction angiography. Magnification arteriography through a catheter in the wedge position has been used in children to determine the nature and extent of pulmonary vascular disease.[204]

Right heart catheterization traditionally has been employed to document severity of pulmonary hypertension, to help establish its cause, to determine the potential for acute pulmonary vasodilatation with oxygen and pharmacologic agents, and to assess the utility of chronic vasodilator therapy.[181] Cardiac chamber pressures are recorded, and the wedge pressure is measured to rule out disease at the level of the left ventricle, left atrium, or large pulmonary veins. Cardiac output is measured and from it and vascular pressures the pulmonary and systemic vascular resistances are calculated. Blood gas samples are taken to determine oxygen contents in the two circulations. These and other variables may be studied at rest or during exercise. Intracardiac shunts may be excluded by the measurements of blood oxygen contents in the various cardiac chambers and by indicator techniques.

Cardiac catheterization in patients with primary pulmonary hypertension usually reveals elevated right atrial pressure, pulmonary arterial pressures that are increased often to systemic levels, and depression of cardiac output. Pulmonary vascular resistance generally is increased, whereas systemic vascular resistance is in the normal range.[135–139, 205] In the United States registry, mean values (±1 SD) were as follows: right arterial pressure, 9.7 ± 6 mm Hg; pulmonary artery pressure, 60 ± 18 mm Hg; wedge pressure, 8.4 ± 4 mm Hg; cardiac index, 2.3 ± 0.9 L/min per m^2; and pulmonary vascular resistance index, 26 ± 14 mm Hg/L/min per m^2.[128] Mixed venous oxygen tensions usually are low, and the arterial-to-mixed venous oxygen content difference is increased. Approximately 20% of patients have a patent foramen ovale. Unless performed carefully, catheterization may increase pulmonary arterial pressure, worsen oxygen transport, and cause death.[206] Because of this possibility, cardiac catheterization should be performed only under controlled conditions, and its risks must be balanced against the information gained.

Virtually identical hemodynamic and clinical findings may be encountered in the extremely rare disease termed *pulmonary veno-occlusive* disease, which accounts for less than 10% of patients with unexplained pulmonary hypertension. Like primary pulmonary hypertension, pulmonary veno-occlusive disease appears to be a morphologic rather than an etiologic entity. In addition, pulmonary veno-occlusive disease tends to afflict infants, children, and young adults, although patients older than 60 years have been reported. However, in the adults with veno-occlusive disease who have been reported, there is a slight male preponderance. A familial occurrence of veno-occlusive disease has also been noted. Veno-occlusive disease has been associated with viral syndromes, toxin exposure, and chemotherapy. The characteristic histologic feature of pulmonary veno-occlusive disease is obstruction of pulmonary venules and veins by intimal fibrosis; intravascular fibrous septa, which are usually considered pathognomonic of recanalized thrombi, are nearly always present.[207] These findings have led to the speculation that thrombosis is an essential pathogenetic mechanism in the great majority of cases, but the factors causing or contributing to thrombus formation are completely unknown.

Of considerable interest is the recent observation that narrowing or obliteration of pulmonary arteries is found in approximately half the cases of pulmonary veno-occlusive disease.[207] The morphologic appearance of the arterial lesions indicated that they were also produced by organization of intravascular thrombi and that the abnormalities were not merely secondary to pulmonary venous obstruction with attendant medial hypertrophy and arterial hypertension. These observations raise the question whether there are two variations of the same basic

disorder: the classic form of pulmonary veno-occlusive disease, in which the arteries are spared, and a generalized form, in which both arteries and veins are involved. It has even been suggested that the latter variety be called *pulmonary vascular occlusive disease*.[208]

Pulmonary veno-occlusive disease cannot be distinguished with certainty from primary pulmonary hypertension by right heart catheterization unless the pulmonary capillary wedge pressure is elevated. Apart from the difficulties of successfully wedging a catheter in patients with pulmonary hypertension, whether or not the wedge pressure is elevated depends on whether the venous obstruction is in the venules or the large veins.[209] This is because the pressure actually measured at the tip of a catheter positioned in an obstructed pulmonary artery, by either wedging or inflating a balloon, is the pressure in the next freely communicating downstream vessel. Accordingly, if venules are occluded, as is often the case in pulmonary veno-occlusive disease, the next freely communicating vessel may be a vein in which the pressure is normal. In contrast, if (large) veins are the sites of occlusion, then the pulmonary venous pressure is likely to be elevated proximally and to be detectable at catheterization. Indeed, the wedge pressure may vary in different sites within the lung in patients with veno-occlusive disease. Some authors have suggested that a diffuse, patchy pattern on perfusion lung scanning in a patient with unexplained pulmonary hypertension is strongly suggestive of pulmonary veno-occlusive disease.[210] The chest radiograph may show signs of pulmonary hypertension with prominent Kerley B lines in the absence of other signs of left heart failure, and this is often the most useful clue to the diagnosis in a patient with unexplained severe pulmonary hypertension. In addition, patients with veno-occlusive disease may develop acute pulmonary edema in response to pharmacologic agents that reduce upstream pulmonary vascular resistance and increase cardiac output, such as prostacyclin.[211] This phenomenon is probably due to an increase in pulmonary blood volume in the face of downstream vascular obstruction.

The final diagnostic technique to be considered in patients suspected of having primary pulmonary hypertension or pulmonary veno-occlusive disease is lung biopsy. In their morphologic study of 156 patients in whom primary pulmonary hypertension was suspected, Wagenvoort and Wagenvoort[144] demonstrated that 45 persons had other disorders, some of which were treatable. More recently, Wagenvoort[212] showed that open lung biopsy may be helpful not only in diagnosing patients but also in predicting their responses to therapy for pulmonary hypertension and congenital cardiac disorders. Despite these studies, open lung biopsy remains a potentially harmful procedure that does not affect the clinical outcome of most patients. Its major value has been in documenting the heterogeneity of lesions in patients with pulmonary hypertension and elucidating the natural history of this condition.

Treatment and Prognosis

A comprehensive medical approach is essential in managing patients with primary pulmonary hypertension. In particular, patients should be instructed to avoid circumstances that may increase pulmonary artery pressure and decrease cardiac output. The alveolar hypoxia of high-altitude (e.g., flying in commercial aircraft) is one stimulus that may exacerbate pulmonary hypertension. Similarly, concurrent cardiopulmonary disease should be treated, oxygen should be given to hypoxemic patients, and cigarette smoking should be avoided. Indomethacin and related prostaglandin synthetase agents and sympathomimetic drugs should be avoided because of their vasoconstrictive actions. So should barbiturates and other drugs that depress cardiac output.[213]

Another potentially adverse circumstance is pregnancy, which imposes an additional burden on the cardiovascular system.[159, 160] Conception probably should be prevented in women with primary pulmonary hypertension, preferably without oral contraceptives, and consideration should be given to terminating pregnancies that occur. If abortion is decided on, abortifacients such as prostaglandin $F_{2\alpha}$, which may increase pulmonary artery pressure, should not be used.[214]

Warfarin has been given to many patients with primary pulmonary hypertension because chronic pulmonary thromboembolism had not been ruled out, because in situ thrombosis was perceived as part of the pathogenesis of primary pulmonary hypertension, or because no other treatment was available. A retrospective review from the Mayo Clinic[215] suggested that anticoagulants actually may have improved survival in patients with pulmonary hypertension of unknown cause, although they often were initiated late in the course of the disease; another more recent review came to the same conclusion.[215a] Whether the improvement was due to alteration of the underlying lesion of plexogenic pulmonary arteriopathy, to treatment of patients who actually had chronic pulmonary thromboembolism or pulmonary veno-occlusive disease, or to preventing in situ thrombosis from becoming superimposed on these three disorders is not clear from these studies. Furthermore, the value of anticoagulation has yet to be established in a prospective randomized trial of patients with either pulmonary hypertension of unknown cause or plexogenic pulmonary arteriopathy in particular. Anticoagulation poses a potential risk, especially in persons prone to syncope or hemoptysis. If anticoagulation is contemplated in such patients, ad-

justed-dose subcutaneous heparin may be considered as an alternative to warfarin. Patients with intracardiac shunting through a patent foramen ovale are at additional risk for a paradoxic embolism.

Vasodilators have been used to treat patients with primary pulmonary hypertension for many years. Most recently, sublingual isoproterenol,[216] phentolamine,[217] hydralazine,[218, 219] diazoxide,[220] nifedipine,[221, 222] captopril,[223] nitrates,[224] and prostaglandin inhibitors[225] have been used on a long-term basis.

The studies of vasodilators in primary pulmonary hypertension are hampered by the lack of a meaningful physiologic end point. Most investigators focus on pulmonary vascular resistance, a variable that is calculated from pressure and flow data rather than measured directly. Pulmonary vascular resistance does indeed decline in some patients receiving vasodilators, but often this decline is due not to a decrease in pulmonary artery pressure but to an increase in cardiac output related to tachycardia, the augmented venous return, and the recruitment of previously unused pulmonary vascular channels. Furthermore, the price paid for a decline in pulmonary vascular resistance may be a fall in systemic vascular resistance associated with severe hypotension and an interference with hypoxic pulmonary vasoconstriction that worsens oxygenation.[226] On the other hand, pulmonary vascular resistance may be a better variable to follow than pulmonary artery pressure. Survival in patients with primary pulmonary hypertension cannot be predicted by the severity of pulmonary hypertension per se and probably is related, as is symptom relief, to increases in transpulmonary blood flow.[183, 227]

Whatever the variable observed, sustained beneficial hemodynamic and symptomatic responses to vasodilators probably occur in 30% to 60% of patients with primary pulmonary hypertension.[141, 228, 229] Because syncope and sudden death may result from vasodilators, these agents should be used cautiously. Furthermore, because hemodynamic response cannot be predicted, the drugs should be administered initially in the catheterization laboratory or under carefully controlled conditions in an intensive care unit. Some investigators have advocated using potent titratable, short-acting intravenous agents such as prostaglandins E_1 or I_2 as screening agents with which pulmonary vasoreactivity can be assessed more safely.[230, 231] Patients receiving vasodilators should be followed closely, and responsiveness should be evaluated by repeat catheterization as required.[232] The most widely used vasodilators are the calcium-channel blocking agents nifedipine and diltiazem.[215a, 228, 233] In responsive patients, these drugs produce improvement in pulmonary hemodynamics and right ventricular function, often accompanied by improved exercise tolerance. Recently, high doses of calcium-channel blockers in patients with primary pulmonary hypertension who responded with reductions in pulmonary artery pressure and pulmonary vascular resistance were shown to improve survival over a 5-year period.[215a] Rich and Brundage[234] have advocated using a regimen consisting of large doses of these agents, which they believe may be required to elicit the sustained beneficial responses. Continuous intravenous infusions of prostacyclin (prostaglandin I_2) have been used in patients who were refractory to conventional therapy, either as a primary mode of treatment or as a bridge to transplantation.[211]

Until recently, combined heart-lung transplantation was the only remaining therapy for patients who did not respond to vasodilators. First performed at Stanford University in 1981, this procedure was associated with both functional improvement and increased longevity in severely disabled persons who would have died without surgery.[235, 236] However, in addition to complications directly related to immunosuppression, such as opportunistic infections and graft rejection, obliterative bronchiolitis occurs with striking frequency in heart-lung transplant patients and can substantially compromise lung function.[236] In addition, organ availability has further limited the widespread application of this technique. (The benefits and complications of lung transplantation are discussed in detail in Chapter 101.)

The remarkable capacity of the right ventricle to revert to normal or near normal function after pulmonary thromboendarterectomy in patients with chronic thrombotic pulmonary vascular obstruction[237] led to the suggestion that single or double lung transplantation may be a viable option for patients with primary pulmonary hypertension who are refractory to medical management. Single lung transplantation has been reported to result in a prompt decline in pulmonary artery pressure and normalization of right heart function in several patients.[238] However, organ rejection may be associated with severe hypoxemia in this setting, owing to an inability to redistribute blood flow to the native hypertensive lung in the setting of impaired ventilation in the donor lung. In addition, obliterative bronchiolitis occurs in lung transplant recipients as well, although the incidence may be lower than in heart-lung transplant patients.

Survival of patients with primary pulmonary hypertension is generally poor, with a median survival in the United States registry of 2.8 years.[128] Variables associated with poor survival included a New York Heart Association functional class III or IV, presence of Raynaud's phenomenon, elevated right atrial and mean pulmonary artery pressures, decreased cardiac index, and decreased diffusing capacity for carbon monoxide.[128] Sudden death occurs frequently, and is probably due to acute right ventricular decompensation, arrhythmia, or a thromboembolic event. Nevertheless, improvements in

management have lengthened survival in the subgroup of patients with reversible pulmonary artery hypertension[238a] and there is hope for other patients with the disease.[239, 240]

SUMMARY

Pulmonary vasculitis is a relatively rare condition despite its association with the collagen vascular disorders and other systemic processes. It is a major component of illnesses such as the granulomatous vasculitides that affect the lungs primarily; it also may be a part of diseases, such as the leukocytoclastic vasculitides, in which the lungs are minimally involved. Because of the considerable overlap among the various pulmonary vasculitides, it seems likely that they have a similar immunopathogenesis. The diagnosis of vasculitis usually is made by biopsy of involved tissues, such as the skin, upper airways, or lungs. Some but not all of these disorders respond to immunosuppressive or cytotoxic drugs. More specific treatment awaits an understanding of the etiology of the pulmonary vasculitides.

Primary pulmonary hypertension is a severely debilitating illness that too often is diagnosed only when it is far advanced. Mortality is related to impaired right ventricular function and is best predicted on the basis of relationships between stroke volume index, and right atrial and pulmonary artery pressures. Iatrogenic insults also contribute to mortality, and clinicians frequently are frustrated both by their inability to treat primary pulmonary hypertension and by complicity in their patients' poor outcome. Despite this frustration, there is reason for cautious hope in primary pulmonary hypertension. Some patients do in fact benefit from vasodilators; others gain extra time with good medical management; still others appear so far to have been helped by combined heart-lung or lung transplantation. The future should bring better tools for the noninvasive assessment of pulmonary hemodynamics and thereby facilitate improved diagnosis and follow-up of patients. Further research also should help elucidate the cause(s) of this baffling disease.

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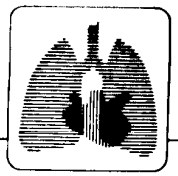

accp consensus statement

Primary Pulmonary Hypertension*

Chairman: Lewis J. Rubin, M.D., F.C.C.P.

(Chest 1993; 104:236-50)

PPH = primary pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; RAP = right atrial pressure

Definitions and Etiology

Primary pulmonary hypertension (PPH), also referred to as unexplained or idiopathic, is a disease or constellation of diseases described at both clinical and pathologic levels. However, neither the clinical syndrome nor the pathologic changes independently define the population with this disease. The vast majority of patients with clinical PPH has a pulmonary arteriopathy, although a few patients will have pathologic evidence of other diseases or even normal lung vessels.[1-4] Pulmonary arteriopathy is not pathognomonic for PPH, because similar changes are also characteristic of patients with congenital heart disease, pulmonary hypertension associated with portal hypertension, toxin-induced pulmonary hypertension, and HIV-related pulmonary hypertension.

For editorial comment see page 5

For practical management, a clinical definition of PPH is sufficient for most patients. A useful clinical definition is the presence of pulmonary hypertension (mean pulmonary artery pressure >25 mm Hg at rest, or >30 mm Hg during exercise), normal pulmonary artery wedge pressure, and absence of secondary causes (Table 1).

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Definition and Description of Pathologic PPH Subsets

Historically, three subsets of PPH have been identified pathologically. However, pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are felt at present to represent distinct entities.

Pulmonary Arteriopathy: In the past, plexogenic pulmonary arteriopathy was considered the hallmark of primary pulmonary hypertension, and plexogenic lesions were considered to be of critical diagnostic and pathogenetic significance. The grading system developed by Heath and Edwards[5] to assess the reversibility of hypertensive vascular lesions in biopsies of patients with congenital heart disease was extrapolated to PPH on the unproven assumption that the pathogenesis and evolution of plexogenic pulmonary arteriopathy would be identical regardless of cause. Several recent studies in large series of patients with clinical PPH have shown that primary pulmonary arteriopathy includes a spectrum of histopathologic lesions ranging from classic plexogenic arteriopathy to microthrombotic, nonplexogenic, forms. The three major types of pul-

Table 1—*Secondary Causes of Pulmonary Hypertension*

Lung disease
• Parenchymal lung disease
• Disorders of ventilation
• Congenital anomalies
• Hypoxia-induced, *ie*, altitude
Heart disease
• Disorders of left heart filling
• Congenital systemic - to - pulmonary shunts
Thromboembolic disease or obstruction of pulmonary vessels
• Pulmonary thromboembolism
• Mediastinal fibrosis
• Congenital stenosis
• Foreign bodies, *ie*, talc
• Tumor
• Hemoglobinopathies
• Schistosome eggs
Collagen vascular diseases and pulmonary vasculitides
Conditions associated with pulmonary hypertension
Exogenous substances
• Anorexic agents
• Toxic rapeseed oil
• L-tryptophan
• Crack cocaine
HIV infection
Portal hypertension

monary arteriopathy involving the muscular arteries are as follow: (1) isolated medial hypertrophy; (2) medial hypertrophy and concentric laminar fibroelastosis, which may or may not be associated with plexiform lesions, angiomatoid lesions, fibrinoid necrosis, and necrotizing arteritis; and (3) medial hypertrophy and eccentric and concentric nonlaminar fibrosis. Plexogenic pulmonary arteriopathy is a nonspecific pattern of response of the pulmonary vasculature to hemodynamic injury, and the Heath-Edwards grading system does not correlate with hemodynamic indices and prognosis.[2]

Pulmonary Veno-occlusive Disease (PVOD): Veno-occlusive disease, an uncommon cause of pulmonary hypertension, was so designated because it was thought to be caused by a primary obstructive thrombotic disorder of the pulmonary venules and veins.[6] Histopathologic changes in the alveolar capillaries and pulmonary arteries were considered to be secondary to venous obstructions. The frequent presence of widespread eccentric and concentric nonlaminar intimal fibrosis of muscular pulmonary arteries in cases of pulmonary veno-occlusive disease suggests that it would be preferable to call this entity obstructive pulmonary angiopathy rather than pulmonary veno-occlusive disease. Although its cause is unknown, similar lesions have been observed in patients treated with certain chemotherapeutic agents,[7,8] and familial cases have been reported.[9,10] As the name indicates, the histopathologic hallmark of this disease is the presence of organized and recanalized thrombi in pulmonary veins and venules. These thrombi are often associated with eccentric fibrous intimal pads not only in venous vessels but also in muscular arteries. The veins show medial hypertrophy and arterialization, the alveolar capillaries are extremely congested, the pleural and peribronchial-perivascular lymphatics are dilated, the pulmonary and pleural interstitium is edematous, and the alveoli contain numerous hemosiderin-laden macrophages. Medial hypertrophy, eccentric and concentric nonlaminar intimal fibrosis, and fibrinoid necrosis of pulmonary arteries are also present.

Pulmonary Capillary Hemangiomatosis (PCH): This is a rare condition characterized by the proliferation of thin-walled microvessels infiltrating the peribronchial-perivascular interstitium, the lung parenchyma, and the pleura.[11] These microvessels infiltrate the walls of pulmonary veins of different diameter, with expansion of the media, fibrous luminal obstruction of the affected vessels, and destruction of the medial elastic fibers. There is also medial hypertrophy of muscular arteries and muscularization of the arterioles. The proliferating thin-walled microvessels are prone to bleeding, resulting in hemoptysis and accumulation of hemosiderin-laden macrophages in alveolar spaces.

Clinical Subsets

Familial PPH: Families with PPH were described soon after the original clinical description of PPH in 1951.[12] Fourteen families with PPH were recorded by 1984,[13] and the NIH registry for PPH recognized familial disease in 12 (6 percent) of 187 patients.[14] The clinical manifestations and outcome of PPH were not different between familial and sporadic patients, except that in familial PPH, the disease was diagnosed earlier after the onset of symptoms, probably due to heightened suspicion.[15] Although the gene predisposing to familial PPH appears to have dominant features, the mode of genetic transmission is complex and has not been definitively established. The genetic analysis of families with PPH is confounded by incomplete penetrance, in which the gene is transmitted by individuals who do not manifest the disease. A few documented instances of father to son transmission of the gene suggested it is not x-linked. An interesting phenomenon, genetic anticipation, in which the age of onset is younger in subsequent generations, is present in many families with PPH. A familial occurrence has been reported for both pulmonary veno-occlusive disease and capillary hemangiomatosis.[9,10,16]

PPH in Children

Although the histopathologic findings in children with PPH are often the same as those in adult patients with PPH, the clinical presentation, natural history, and factors influencing survival may differ. These differences appear to be most apparent in the younger children. Syncope, with or without seizures, is a frequent presenting symptom in young children and is more often effort-related in children than in adult patients with PPH. Right heart failure is rare in the younger children, occurring most often in children over 10 years of age with severe, long-standing PPH. Childhood PPH occurs with equal frequency in female and male children as opposed to 1.7:1 female to male ratio seen in adult patients.[14] The interval between onset of symptoms and time of diagnosis is usually shorter in children than in adults, particularly in those children who present with syncope.

Prior to the era of vasodilator treatment for PPH, most children died within 1 year of diagnosis as opposed to the 2- to 3-year median survival in adult PPH patients. The age at diagnosis appears to be the most important predictor of survival in children. The hemodynamic parameters (mean pulmonary artery and right atrial pressures and cardiac index) that are useful in predicting survival in adult patients with PPH may not be applicable to the pediatric population. Baseline hemodynamics are often similar in the younger and older children, although chronic vasodilator responses as well as long-term survival differ significantly.[17] Histopathologic studies offer clues to

the findings. In the classic studies by Wagenvoort and Wagenvoort,[4] not only was medial hypertrophy severe in patients under 15 years of age, but it was also often the only change in infants, suggesting a more vasoreactive pulmonary vascular bed in the youngest children. The youngest children also tend to respond better to long-term vasodilator treatment. Higher doses (per kilogram) of calcium channel blockers may be needed to produce a favorable response in children with PPH compared to adult patients.[18]

Conditions Associated With Pulmonary Vasculopathy

Exogenous Pulmonary Hypertension: Drug-Induced Pulmonary Hypertension

(a) Anorexic agents (aminorex, fenfluramine): An epidemic of chronic pulmonary hypertension occurred in Switzerland, Austria, and Germany in the late 1960s in association with the use of aminorex (2-amino-5-phenyl-2-oxazoline), an appetite suppressant with a chemical structure similar to adrenaline and ephedrine.[19] This drug was released into the market in Switzerland in 1965 and was withdrawn in 1968. A 20-fold increase in the incidence of chronic pulmonary hypertension started in 1967, peaked from 1968 to 1969, and disappeared after 1972. The association of the epidemic of pulmonary hypertension with the use of aminorex is strong relative to geographic distribution and timing, but the exact relationship is not understood, and the mechanism remains unsolved. Estimates suggest that only 1 out of 1,000 users of aminorex developed pulmonary hypertension. However, the incidence of pulmonary hypertension also was increased in individuals who did not report the use of aminorex, and the disease syndrome could not be reproduced in animals, even after trials in several species in whom aminorex was administered for up to 2 years.

The pathologic condition of aminorex-associated pulmonary hypertension is indistinguishable from idiopathic pulmonary arteriopathy. The reported cases were characterized by medial hypertrophy of muscular arteries and muscularization of arterioles, concentric laminar intimal fibrosis, plexiform and angiomatoid lesions, fibrinoid necrosis, and siderosis.

Four patients have been reported[20,21] with pulmonary hypertension which developed subsequent to the use of fenfluramine or dexfenfluramine (N-ethyl and methyl 3(trifluromethyl) benzene-ethanamine hydrochloride), a sympathomimetic amine in current use as an appetite suppressant.

(b) L-tryptophan-associated pulmonary hypertension: An epidemic characterized by a syndrome of diffuse myalgia and eosinophilia was first recognized in New Mexico in 1989. The eosinophilia-myalgia syndrome (EMS) was soon linked to consumption of L-tryptophan, which was available over the counter for insomnia, depression, or premenstrual syndrome. More than 1,400 EMS cases have been reported to the Center for Disease Control, including several deaths. Common clinical manifestations have included myalgia, arthralgia, dyspnea, and cough. Pulmonary disease syndromes have included diffuse pulmonary infiltration, pleural effusion, and pulmonary hypertension. The mechanism is unknown, but it is suspected to be the result of a toxic byproduct or contaminant of L-tryptophan. An analogy has been suggested between the symptom complex of EMS and that of the toxic oil syndrome. Both epidemics included patients with progressive polyneuropathy, pulmonary hypertension, vasculitis, embolic phenomena, and death.

Lung biopsies from five patients[22] showed widespread nonnecrotizing vasculitis involving both arteries and veins. The vasculitis was characterized by dense perivascular and transmural infiltrates of lymphocytes and few eosinophils. In three patients, there was also fibromyxoid intimal thickening of muscular pulmonary arteries and veins. The vascular pathologic condition was associated with mild interstitial pneumonia with interstitial accumulation of lymphocytes and eosinophils.

(c) Chemotherapy-related pulmonary hypertension: Several patients with PVOD developing after chemotherapy have been reported. Some of the implicated agents include carmustine, bleomycin, cyclophosphamide, etoposide and mitomycin-C.[7,8]

(d) Crack cocaine inhalation: A recent report cited four young women who developed clinical pulmonary hypertension and hypertensive changes in muscular pulmonary arteries in association with smoking crack cocaine.[23] The authors suspected a predisposition for disease in females, since the majority at risk were males.

Exogenous Pulmonary Hypertension: Toxins

(a) Toxic oil syndrome: The toxic oil syndrome is a multisystem disorder which was related to the consumption of an illegally marketed rapeseed cooking oil in Spain in 1981.[24] More than 20,000 cases were reported, and many deaths were related to pulmonary hypertension. The syndrome had several stages, with an early systemic syndrome that included respiratory distress and pulmonary infiltrates, which was followed by a second stage in which one third of the patients developed fever, myalgias, and neurologic symptoms. Pulmonary hypertension was a common problem in this second stage. A later stage appeared similar to scleroderma, with weight loss and neuromuscular disorders. In 1986 and 1987, severe pulmonary hypertension was the leading cause of death from toxic oil syndrome.[25] The specific toxic agent has not been identified, but oleoanilides or toxic compounds derived from them or both are believed to be important.

The pathology is unique but most closely resembles

pulmonary veno-occlusive disease, both arteries and veins are involved. The initial lesions consist of endothelial injury with marked proliferation of myoendothelial cells and vasoformative reserve cells and perivascular inflammatory infiltrates. The intimal lesions subsequently evolve into obliterative intimal and luminal fibrosis of arteries and veins. Medial hypertrophy of muscular arteries, muscularization of arterioles and even plexiform lesions have been reported.

(b) Portal Hypertension-Associated Pulmonary Hypertension: Although numerous reports during the last four decades suggested an association of pulmonary hypertension with portal hypertension, the relationship is sufficiently infrequent that its existence has been debated. A large autopsy series first demonstrated conclusively that the relationship is real; McDonnell et al[26] reviewed 17,901 autopsies at Johns Hopkins from 1944 to 1981 and found that PPH occurred in 0.13 percent of all patients, but in 0.73 percent of patients with cirrhosis ($p<0.001$). Of 2,459 clinical patients with biopsy-proven cirrhosis, the clinical prevalence of PPH was 0.61 percent ($p<0.001$).

A recent prospective study[27] substantiated the increased incidence of pulmonary hypertension in cirrhosis by finding that 10 (2 percent) of 507 patients hospitalized with portal hypertension had PPH. The mechanisms are unclear, but portal hypertension, rather than cirrhosis itself, appears to be the prerequisite for development of pulmonary hypertension.

Pathologically, patients with portal hypertension, with or without cirrhosis, have been reported to have pulmonary arteriopathy either of the plexogenic type or of the microthrombotic type.

(c) HIV Infection-Associated Pulmonary Hypertension: Several case reports have described patients with HIV infection who developed the clinical syndrome of PPH. One early report[28] described five patients with hemophilia who developed PPH; all had received intravenous factor VIII for several years and tested positive for HIV. In individuals who develop HIV infection related to intravenous drug use, there is additional concern that pulmonary vascular obstruction from embolic material or talc granulomatosis may be contributory. A recent prospective study[29] reported 74 patients from a cohort of 1,200 patients who were positive for HIV. Six patients developed pulmonary hypertension, supporting an association of PPH and HIV positivity.

Pathogenesis and Pathophysiology

Pathogenesis

The pathogenesis of PPH remains speculative. Figure 1 shows the suggested mechanisms responsible for the pathogenesis of this disease. The most widely accepted proposed mechanism for the pathogenesis of PPH-pulmonary vasoconstriction is based on histo-

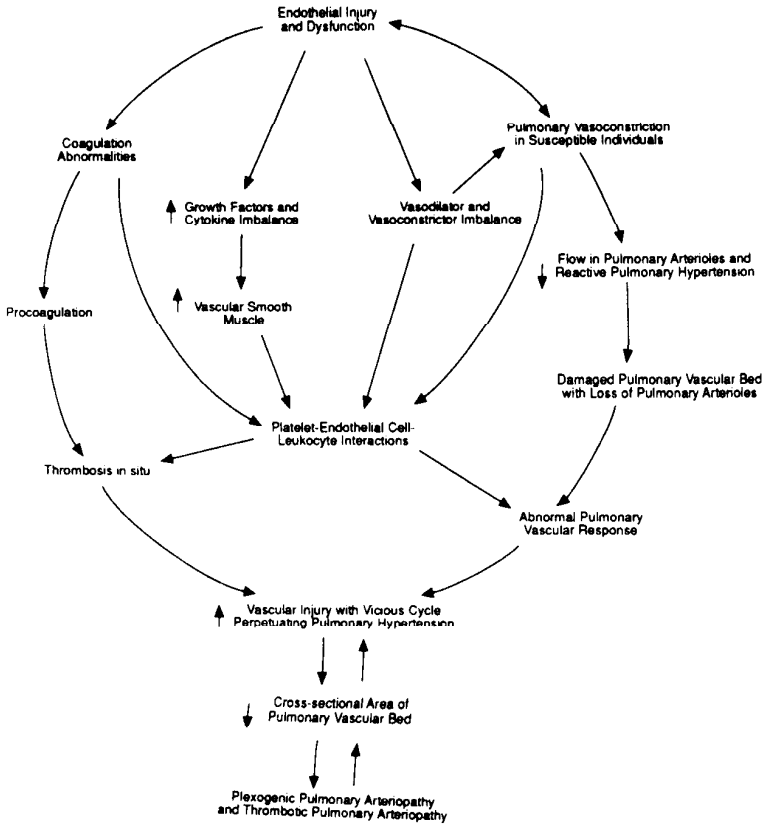

FIGURE 1. Possible pathogenesis of PPH.

pathologic studies and clinical responses to vasodilator therapy.[1,18,30,34] These studies suggest that PPH is a disease of predisposed individuals, in whom various stimuli may initiate the development of the characteristic vascular lesions. Whether or not vasoconstriction is the *primary* event in the pathogenesis of PPH, it is an important component in its pathophysiology. Possible triggers of pulmonary vasoconstriction in susceptible individuals include the following: normobaric or hypobaric (high altitude) hypoxia, autoimmune disorders, drugs and toxins, increased pulmonary blood flow with or without increased pressure and shear stress, lung injury, and increased sympathetic tone resulting in catecholamine-induced injury.[35-41] Many of these vasoconstrictor stimuli can damage the pulmonary endothelium, resulting in alterations in the balance between vasoactive mediators. Several studies have looked at the possible role of an imbalance favoring vasoconstrictor mediators including thromboxane versus prostacyclin,[42-44] and other endothelial-derived factors.[45,46] Coagulation abnormalities may occur, initiating or further exacerbating the pulmonary vascular disease.[47,48] For example, elevated levels of thromboxane promote not only pulmonary vasoconstriction, but also activate platelet aggregation. The interactions between the humoral and cellular elements of the blood and an injured endothelial cell surface result in remodeling of the pulmonary vascular bed and may contribute to the process of vascular injury.[49,50]

Migration of smooth muscle cells in the pulmonary arterioles occurs with release of an unidentified chemotactic agent from injured pulmonary endothelial cells.[51] Endothelial cell damage can also produce thrombosis *in situ*, transforming the pulmonary vascular bed from its usual anticoagulant state (due to release of prostacyclin and plasminogen activator inhibitors) to a procoagulant state.[52] Fibrinopeptide A levels are elevated in patients with PPH suggesting that *in situ* thrombosis is occurring.[53] Further support for the role of coagulation abnormalities at the endothelial cell surface in the pathogenesis of PPH comes from the demonstration that treatment with anticoagulation therapy has also resulted in increased survival.[34]

Pathophysiology

The normal pulmonary circulation is a high flow, low resistance, circulation. During exercise, pulmonary blood flow increases and pulmonary vascular resistance decreases due to both recruitment of unopened vessels and distension of patent pulmonary blood vessels. These two normal adaptations prevent marked increases in pulmonary artery pressure even when pulmonary blood flow increases by three- to fivefold. The normal right ventricle is a thin-walled, distensible muscular pump that accommodates to considerable variations in systemic venous return without large changes in filling pressures.

With pulmonary artery hypertension, the right ventricle hypertrophies in response to the prolonged pressure overload. Pulmonary hypertension without right ventricular failure occurs with a normal cardiac output and a normal right ventricular filling pressure at rest as well as during exercise. With prolonged pulmonary hypertension, an anatomic decrease in cross-sectional area and distensibility of pulmonary resistance vessels occurs in addition to vasoconstriction of pulmonary resistance vessels. Initially, the cardiac output remains normal at rest but does not increase appropriately with exercise, despite an increase in right ventricular filling pressure. Right ventricular myocardial blood flow may be compromised by increases in right ventricular systolic and diastolic pressures and heart rate, producing right ventricular ischemia. Eventually, the cardiac output becomes decreased at rest. Right ventricular volume overload develops with tricuspid regurgitation, leading to increasing right ventricular wall stress and contributing to failure. Severe right ventricular hypertension also affects left ventricular diastolic function, increasing left ventricular end diastolic pressure and decreasing left ventricular filling. The pulmonary capillary wedge and left ventricular filling pressures may be modestly increased in this setting.

Syncopal episodes in PPH are usually effort-related and are due to a limitation in cardiac output. Other mechanisms, including sympathetic and parasympathetic alterations, may also play a role.

Based on the pathogenesis and pathophysiology of PPH, the two most frequent mechanisms of death are progressive right ventricular failure and sudden death, with the former occurring more often.[54] With progressive right ventricular failure, the scenario as described above leads to dyspnea, hypoxemia, and a progressive decrease in cardiac output. Pneumonia commonly is fatal due to alveolar hypoxia causing further pulmonary vasoconstriction, with an inability to maintain adequate cardiac output and resulting in cardiogenic shock and death. When arterial hypoxemia and acidosis occur, life-threatening arrhythmias may also develop. Postulated mechanisms for sudden death with PPH include the following: bradyarrhythmias and tachyarrhythmias, acute pulmonary embolus, massive pulmonary hemorrhage, and sudden right ventricular ischemia.

Diagnosis

Although the diagnosis of PPH is one of exclusion, it can be made with a high degree of accuracy if care is taken to exclude all likely secondary causes. A thorough and detailed history and physical examina-

Table 2—*Evaluation of Unexplained Pulmonary Hypertension

	Data Obtained	Risk†	Information Quality	Secondary Causes Detectable
Screen				
History	Dyspnea, angina, syncope	0	+ + + +	PE, CHD, lung disease, LV dysfunction
Physical Exam	$^{*}P_2$, RV lift, clubbing	0	+ + + +	Lung disease, CHD
CXR	Heart size, lung parenchyma, vascular pattern	0	+ +	Lung disease, PVOD, LV dysfunction
ECG	RVH	0	+ +	CHD
Diagnose				
Echo	Shunts, valves, LV function, PA pressure	0	+ + + +	CHD, valve disease, LV dysfunction
V/Q scan	Lobar, segmental perfusion	0	+ + +	Chronic thromboembolism
PFTs	Lung function	0	+ + +	Parenchymal disease
ABG	P_{O_2}, P_{CO_2}	+	+ + +	Hypoxemia, hypoventilation
Confirm/Refine				
Catheterization	Pressures, shunts, flow	+	+ + + +	PVOD, CHD
Pulmonary angiography	Vascular anatomy	+	+ + +	PE, pulmonary stenoses
CT/MRI	Central pulmonary vascular anatomy, parenchyma	0	+ + +	Proximal PE, lung disease
Angioscopy	Intraluminal anatomy	+ +	+ + +	Proximal PE
Lung biopsy	Histopathology	+ +	+ +	Vasculitis, PVOD
Serologies	ANA, RF, CH_{50}	0	+	Vasculitis, collagen vascular disease
Management				
Catheterization	Dose-response	+	+ + + +	Drug efficacy & safety, prognosis
Echo	RV size, function	0	+ +	Drug efficacy treatment response
Exercise Study	Quantitate exercise tolerance	+	+ +	Treatment response

*Abbreviations: PE = pulmonary embolism; CHD = congenital heart disease; PVOD = pulmonary venocclusive disease; LV = left ventricle; RV = right ventricle; RVH = right ventricle hypertrophy; PA = pulmonary artery; CT = computerized tomography; MRI = magnetic resonance imaging.

†Note: risk of performance and information quality are rated on a scale of 0 to 4 + .

tion, as well as appropriate tests, must be performed to uncover potential causative or contributing factors, many of which may not be readily apparent (Table 2). In the National Institutes of Health registry on PPH, an algorithm was developed listing essential tests and secondary diagnoses to be excluded[14] (Fig 2). No patient with a secondary cause of pulmonary hypertension was diagnosed as having PPH in the registry when this algorithm was followed.

Presenting Symptoms

The most common symptom of PPH is dyspnea, which is the initial symptom in 60 percent of patients and is eventually present in virtually all patients. Syncope may also be an early symptom of PPH (8 percent). In contrast to the older literature, current experience suggests that Raynaud's phenomenon occurs with no greater frequency than in the general population. Angina is also common (47 percent). Edema is generally a reflection of right ventricular failure and is more likely to be associated with advanced disease. The time of onset from the first symptom until diagnosis in the NIH registry was 2.03 ± 4.9 years,[14] indicating that the diagnosis is generally made late.

Physical Examination

The physical findings of patients with PPH are

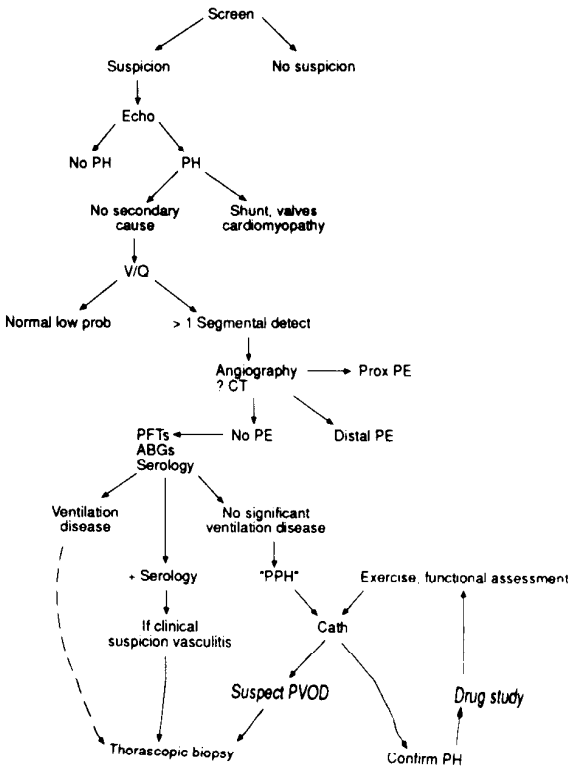

FIGURE 2. Algorithm for diagnosis of PPH. V/Q = ventilation/perfusion; PFTs = pulmonary function tests; ABGs = arterial blood gas determinations; and CATH = right heart hemodynamic catheterization.

typical of any patient with pulmonary hypertension. An increase in the pulmonic component of the second heart sound and a right-sided fourth heart sound are early findings. Tricuspid regurgitation is also very common. A right ventricular third heart sound generally reflects advanced disease. Pulmonic insufficiency may be heard and usually relates to dilatation of the main pulmonary artery. Peripheral cyanosis and edema are often seen. Edema is a sign of right ventricular dysfunction. Clubbing is not a feature of PPH and should suggest an alternative diagnosis.

Diagnostic Evaluation

The Electrocardiogram: The electrocardiogram commonly shows right axis deviation and right ventricular hypertrophy with secondary T-wave changes but does not necessarily parallel the severity of the underlying pulmonary hypertension.[55] Atrial fibrillation is a particularly uncommon rhythm in PPH and may not be well-tolerated because of the dependence upon atrial systole for ventricular filling.[56]

Imaging: Chest Radiograph. The chest radiograph shows evidence of pulmonary hypertension in over 90 percent of cases.[14] Prominence of the main pulmonary artery occurs in 90 percent, hilar vessel enlargement in 80 percent, and pruning of the vessels with hyperlucent lung periphery in 51 percent. While a completely normal chest x-ray film speaks against the diagnosis, it should be noted that 6 percent of patients with PPH enrolled in the NIH registry had a normal radiograph.[14]

Echocardiography. The echocardiogram can be useful to look for myocardial dysfunction, valvular disease, or congenital heart disease. The typical echocardiographic appearance of the patient with PPH shows right ventricular and right atrial enlargement with a normal to reduced left ventricular cavity.[57] Pulmonic and tricuspid insufficiency is also easily detected with Doppler interrogation. Reversal of the normal septal curvature associated with right ventricular pressure overload states is seen in advanced disease.[58] Hemodynamic correlations between the pulmonary vascular resistance and echocardiographic findings reveal an inverse relationship between left ventricular internal dimension and pulmonary vascular resistance, suggesting that underfilling of the left ventricle is a reflection of the severity of the pulmonary vascular disease. Doppler studies have also shown a redistribution of left ventricular filling from early to late diastole as a reflection of reduced compliance of the left ventricle.[56] Doppler ultrasound can be used to noninvasively determine the pulmonary artery pressure. Most commonly, the magnitude of the tricuspid regurgitant flow velocity can be determined and enhanced using saline solution contrast to give relatively reproducible measurements of the right ventricular systolic pressure.[59] Pulmonic valve insufficiency is frequently seen, and characteristics of the pulmonic regurgitant flow velocity or changes in the systolic flow velocity profile across the pulmonic valve can also be used to estimate pulmonary artery pressure noninvasively.[60,61] Recently, transesophageal echocardiography has been employed in the evaluation of patients with pulmonary hypertension.[62] It has an advantage of offering precise assessment of intracardiac defects and is very sensitive in the detection of a patent foramen ovale.[63]

Ventilation-perfusion scintigraphy. It is mandatory that patients with pulmonary hypertension undergo ventilation-perfusion lung scanning in order to rule out chronic thromboemboli as the cause of the elevated pulmonary artery pressure. In PPH, the lung scan is either normal or low probability with small, patchy defects.[14] Conversely, in thromboembolic pulmonary hypertension, the lung scan demonstrates at least one major ventilation-perfusion mismatch, often two or more.[64] Therefore, a normal or low probability lung scan rules out thromboembolic pulmonary hypertension, and no further workup is necessary in this regard.

Pulmonary angiography. If the lung scan shows one or more segmental, or greater, ventilation-perfusion mismatches, an angiogram should be performed to rule out thromboembolism. While care should be exercised, pulmonary hypertension is not a contraindication to pulmonary angiography. In thromboembolic pulmonary hypertension, the clots are actually incorporated into the wall of the pulmonary artery and endothelialized so the angiogram may underestimate the extent of obstruction or be difficult to interpret. It may be necessary to employ angioscopy or magnetic resonance imaging in these cases. Angioscopy has had very limited application and is performed in few centers. It should not be performed except in those centers with considerable experience in the diagnostic evaluation of thromboembolic pulmonary hypertension.

Radionuclide angiocardiography. Radionuclide angiography can be utilized to assess both left and right ventricular function. However, caution should be taken in interpreting right ventricular ejection fractions in the presence of large right atrial and ventricular chambers, as true isolation of the right ventricular blood pool can be difficult. Right ventricular ejection fraction has been shown to be inversely proportional to the pulmonary artery pressure, although direct estimation of pulmonary artery pressure from the right ventricular ejection fraction is difficult.

MRI and ultrafast CT. As newer generations of MRI and CT scanners have evolved and software has improved, these imaging techniques have begun to offer great promise. Thrombi in proximal pulmonary arteries can be visualized without the necessity of an

angiogram.[65] In addition, ventricular and septal wall motion can be evaluated with calculation of right and left ventricular ejection fractions.[66] The sensitivity of these tests for detection of central clots sufficient to cause pulmonary hypertension has not been determined, but this may become part of the diagnostic algorithm for PPH in the near future.

Pulmonary Function Testing: Abnormalities of pulmonary function may be present in PPH, particularly in the more advanced stages of the disease. The functional abnormalities may reflect derangements in either the mechanical or gas exchanging properties of the lung, with changes in the latter tending to be more prominent and disproportionately greater.

The functional abnormalities described in PPH include mild restrictive defects, small airways dysfunction, reduced carbon monoxide diffusing capacity (D_{CO}), and impaired gas exchange as reflected by hypoxemia, hypocapnia (alveolar hyperventilation), and increased alveolar-arterial $(A\text{-}a)O_2$ gradient. Pulmonary function studies performed on the 187 patients in the PPH registry disclosed only mild reduction in lung volumes and no evidence of airways obstruction.[14] The presence of moderate or severe restrictive or obstructive physiologic defects should suggest another diagnosis. Severe hypoxemia can occur in PPH, due *either* to intracardiac shunting via a patent foramen ovale or a severely depressed cardiac output with resultant mixed venous hypoxemia.

Cardiopulmonary Exercise Tests: Cardiopulmonary exercise tests are useful in the evaluation of patients with nonapparent causes of dyspnea since there is a characteristic pattern of ventilatory and circulatory response in the presence of pulmonary vascular disease.[67] Since their sensitivity and specificity in the diagnosis of pulmonary hypertension are unknown, exercise testing is not considered essential in the evaluation of a patient with suspected PPH.

Connective Tissue (Collagen Vascular) Serologic Studies: Elevations in antinuclear antibodies are common in PPH and do not necessarily imply an associated collagen vascular disease. No specific pattern of antinuclear antibodies or titer has been consistently associated with PPH. As all of the collagen vascular diseases have been associated with pulmonary hypertension, it is possible that some patients with PPH have a collagen vascular disease that is confined to the lung.

Lung Biopsy: Lung biopsy is not considered essential in making an accurate diagnosis of PPH. In selected patients, a lung biopsy may be desirable or necessary to establish a diagnosis when confounding factors make the diagnosis otherwise uncertain. In that respect, an accurate diagnosis distinguishing the patient as having primary or secondary pulmonary hypertension may be very important with respect to prognosis and management. Transbronchial lung biopsy is of no value in the diagnosis of primary pulmonary hypertension because it does not sample blood vessels adequately and may also be risky due to elevated pulmonary artery pressure. Open lung biopsy, possibly using a thoracoscope, would be preferred. Care should be taken in obtaining the tissues, preferably from right or left lower lobes during full lung inflation. A correct histologic diagnosis can be difficult, and the pathologic material should be referred to a pathologist with expertise in pulmonary vascular disease.

Cardiac Catheterization: Cardiac catheterization is an absolute requirement for confirming the diagnosis of PPH and for guiding management. Particular care should be taken to exclude intracardiac shunting and accurately ascertain left ventricular filling pressure with either a pulmonary capillary wedge pressure determination or directly with left ventricular catheterization. It should be recognized that left ventricular filling pressures may rise modestly in severe PPH due to diastolic dysfunction related to the pulmonary hypertension. Pulmonary veno-occlusive disease can result in a gradient between the wedge pressure and left ventricular end-diastolic pressure, although the wedge pressure is usually normal or only mildly elevated. Typical of veno-occlusive disease is variability in wedge pressure determinations from various sites within the lung. Particular attention should be paid to the accurate measurement of the right atrial pressure, pulmonary artery pressure, and cardiac output, since they specifically relate to prognosis. Although the direct measurement of cardiac output through the Fick method is preferred in low cardiac output states, a reasonably accurate assessment using thermodilution can be obtained in most patients. Flow-directed catheters for the right side of the heart with an internal guidewire are commercially available and have been particularly helpful in positioning the catheter in the pulmonary artery.

Therapy

There is no cure for PPH, nor is there a therapeutic approach which is uniformly accepted or successful. However, treatment for this disease has improved dramatically over the past decade, resulting in sustained clinical improvement and prolongation of life in a substantial percent of patients. This section will address the management of PPH.

General Measures

Because PPH is a rare disease whose complexity poses tremendous challenges to the treating physician, it is recommended that patients be referred to a center with experience in management of this disease. The referring physician must, nevertheless, play a major

role in the day to day care of these patients, and an ongoing dialogue between the treating physicians is crucial.

Patients with PPH should avoid circumstances or substances which may aggravate the disease state. For example, exercise should be guided by symptoms, and exposure to high altitude may worsen pulmonary hypertension by producing alveolar hypoxia-induced pulmonary vasoconstriction. While airplane travel is generally safe, supplemental oxygen therapy may be advisable, particularly when flying in nonpressurized cabins or when patients are mildly or moderately hypoxemic at sea level. Additionally, pregnancy should be avoided since this is poorly tolerated in the setting of PPH. Since oral contraceptives may worsen pulmonary hypertension, other effective methods of birth control should be used.

Supplemental Oxygen Therapy

Alveolar hypoxia frequently occurs in the setting of long-term parenchymal lung disease, and hypoxic pulmonary vasoconstriction contributes to the pathogenesis of pulmonary vascular disease in this setting. Supplemental low-flow oxygen alleviates arterial hypoxemia and attenuates pulmonary hypertension in patients with these disorders; in contrast, most patients with PPH do not exhibit resting hypoxemia and derive little hemodynamic benefit from supplemental oxygen therapy.[68] Some patients, however, will experience arterial oxygen desaturation with activity, due to increased oxygen extraction in the face of fixed oxygen delivery, and these patients may benefit from ambulatory supplemental oxygen. Patients with severe right-sided heart failure and resting hypoxemia, resulting from a markedly increased oxygen extraction even at rest, should be treated with continuous oxygen therapy. The goal of oxygen therapy is to maintain an arterial oxygen saturation above 90 to 92 percent. Patients with hypoxemia solely resulting from a right-to-left shunt through a patent foramen ovale characteristically do not improve their level of oxygenation to an appreciable degree with supplemental oxygen.

Cardiac Glycosides

The efficacy of cardiac glycosides in PPH is unknown. There is little evidence that these drugs are useful in patients with isolated right ventricular dysfunction associated with chronic lung disease.[69] Furthermore, the risk of digitalis toxicity may be enhanced if hypoxemia and diuretic-induced hypokalemia are also present. Some authors have advocated the use of digitalis concomitant with calcium channel blockers in PPH in order to counteract the potentially negative inotropic effects of the latter.[33]

Diuretics

Diuretics can be quite useful in reducing the increased intravascular volume and hepatic congestion which occur in patients with right-sided heart failure. However, the right ventricle is highly dependent on preload, and great care should be taken to avoid excessive diuresis in these patients since this can lead to a fall in cardiac output and can compromise the use of other pharmacologic measures such as vasodilators. Diuretic therapy may be instituted with low doses of furosemide (20 to 40 mg/d) and increased as needed, monitoring volume status by physical examination and laboratory data. Patients who are refractory to doses of furosemide of greater than 120 mg/day may be treated with metolazone as an adjunct. Meticulous monitoring of serum electrolytes is mandatory, and potassium or magnesium supplementation may be necessary when these agents are used.

Anticoagulant Therapy

Patients with severe pulmonary hypertension are at risk for thrombotic events due to their sedentary lifestyle, venous insufficiency, dilated right-sided heart chambers, and sluggish pulmonary blood flow. Even a small pulmonary vascular obstruction by thrombus can be life-threatening in a patient with a compromised pulmonary vascular bed which possesses little ability to dilate or recruit unused vessels. Indeed, patients with PPH frequently die suddenly, and fresh intrapulmonary clot may be found at post-mortem examination. Thus, anticoagulation as a prophylaxis for thromboembolism may be justified in patients with PPH. A retrospective study from the Mayo Clinic provided support for this concept. Patients with PPH who received anticoagulants manifested improved survival when compared with those who were not treated with anticoagulants.[70] Recently, Rich et al[34] demonstrated in a small prospective study that anticoagulation was associated with significant improvement in survival rates.

The preferred approach to anticoagulation is to administer warfarin in doses sufficient to prolong the prothrombin time to approximately 1.3 to 1.5 times control (international normalized ratio of 2.0 to 3.0). Patients should be advised regarding the risks and dangers of anticoagulation therapy and should avoid using nonsteroidal agents or any medication which could alter the effects of warfarin. Since right-sided heart failure may impair hepatic function, monitoring of the anticoagulant effects of warfarin in this setting must be done with greater frequency.

Adjusted-dose heparin, using doses which prolong the partial thromboplastin time to 1.3 to 1.5 times control, is a suitable alternative to warfarin, although its use is more cumbersome. This approach may be considered in patients who have a greater risk for hemorrhagic events, such as prior episodes of hemoptysis, or who have had adverse effects with warfarin,

such as alopecia.

Vasodilators

The rationale for the use of vasodilator agents to treat pulmonary hypertension is based on the premise that pulmonary vasoconstriction is present, to varying degrees, in this disease, and that even small reductions in right ventricular afterload will produce substantial improvement in right ventricular output. This concept is supported by the pathologic finding of medial hypertrophy of the muscular pulmonary arteries as an early and consistent feature of PPH.[4,71] There is no selective pulmonary vasodilator agent, although a variety of systemic vasodilators have been demonstrated to produce pulmonary vascular effects in experimental and clinical conditions (Table 3).

The goal of vasodilator therapy for PPH is to reduce pulmonary artery pressure and increase cardiac output without symptomatic systemic hypotension. This effect may be achievable in approximately one fourth of patients. Rich and Brundage[33] have reported that calcium channel blockers can produce sustained reductions in pulmonary artery pressure and regression of right ventricular hypertrophy in such patients.

In approximately one half of PPH patients, vasodilators will increase cardiac output without affecting pulmonary artery pressure.[72] While exercise tolerance and right ventricular function may be improved in these patients, the long-term effects on survival are unknown. Furthermore, whether this effect can be sustained for prolonged periods of time is unclear.

In the remaining one fourth of patients, vasodilators either reduce systemic pressure without altering pulmonary artery pressure or cardiac output, or increase pulmonary artery pressure commensurate with an increased output. These patients are felt to have "fixed" vascular disease, and vasodilator therapy is contraindicated.

Patients with pulmonary veno-occlusive disease may develop life-threatening pulmonary edema in response to vasodilator administration, presumably as a result of increasing pulmonary blood flow in the presence of persistent downstream vascular obstruction.[73]

There are no hemodynamic or demographic variables which predict vasoreactivity. Patients with symptoms for several years suggestive of severe pulmonary vascular compromise, such as syncope, may manifest near-complete reversibility with vasodilators, while others with a brief duration of symptoms may have irreversible disease. This observation underscores the great variability in the course of this disease and serves to emphasize the need to individualize the approach to therapy for each patient. The experience from the NIH registry on PPH has suggested, however, that patients with right-sided heart failure, defined as an elevated right atrial pressure, are at the greatest risk for adverse events when a long-acting nontitratable vasodilator is administered immediately.[72]

Table 3—*Dose Ranges, Route of Administration, and Half-Lives of Most Frequently Used Vasodilators*

Drug	Route	Dose Range	Half-Life
Nifedipine*	Oral	30-240 mg/day	2-5 h
Diltiazem*	Oral	120-900 mg/day	2-4.5 h
Prostacyclin†	Intravenous	2-24 ng/kg/min	3 min
Prostaglandin E_1	Intravenous	5-30 μg/kg/min	2-4 min

*Sustained release preparations (Procardia XL and Cardizem CD) may be given once daily; half-life shown refers to conventional preparation.

†Dose range listed is for immediate infusions; dose requirements and tolerance in patients receiving long-term infusions have increased over time, often exceeding 50 to 100 ng/kg/min.

The approach taken in many centers is to use a potent, short acting, titratable vasodilator such as immediate intravenous infusion of prostacyclin (prostaglandin I_2) during right-sided heart catheterization to determine the potential and magnitude of vasoreactivity.[74] The advantages of prostacyclin in this setting are its potency as a pulmonary vasodilator, its titratability, and its short half-life (3 to 5 min). Prostacyclin is administered in incremental doses from 1 to 12 ng/kg/min, monitoring systemic and pulmonary hemodynamics, cardiac output, and arterial saturation. The responses to prostacyclin have been useful in determining which patients may respond to oral therapy.[18,75] Prostacyclin is not commercially available in the United States at the present time; alternatives which may be suitable for testing acute reactivity include acetylcholine, prostaglandin E_1, and adenosine.

Patients who manifest a potentially beneficial response to acute vasodilator challenge defined as either a reduction in pulmonary artery pressure with no change or an increase in cardiac output, or an increased cardiac output with an unchanged pulmonary artery pressure, may be treated with oral calcium channel blockers. A common strategy is to titrate nifedipine with hourly doses until maximal hemodynamic effects or adverse effects are achieved. Sustained release nifedipine (Procardia XL) in doses of 120 to 240 mg/day is often used. In some patients who either have a resting tachycardia or develop unacceptable systemic hypotension with nifedipine, diltiazem, in doses up to 900 mg daily, is a suitable alternative. The heart rate and PR interval on electrocardiogram should be monitored in patients receiving diltiazem, since bradycardia and atrioventricular block may occur. Verapamil is not recommended for use in PPH since it has a greater propensity to produce negative inotropic effects. Additionally, unmonitored empiric treatment with any vasodilator is strongly discouraged.

The major adverse effects of calcium channel blocker therapy in PPH are reduction in cardiac output due to the negative inotropic effects, systemic hypo-

tension, and edema due to salt and water retention. When edema develops in a PPH patient receiving calcium channel blocker therapy, it is important to differentiate between the effects which these agents have on renal salt and water reabsorption and right heart failure due to negative inotropy. Vasodilators can also produce arterial hypoxemia through the following three mechanisms: increasing blood flow to poorly ventilated lung units (decreasing V/Q matching); increasing right to left shunting through a patent foramen ovale if a greater degree of systemic vasodilation than pulmonary vasodilation is produced, and decreasing mixed venous oxygen content if cardiac output actually falls. The first scenario occurs more commonly in patients with pulmonary hypertension secondary to underlying parenchymal lung disease, while right-to-left shunting through a patent foramen ovale is present only in more severe forms of pulmonary hypertension. A similar phenomenon may occur in patients with Eisenmenger's physiology who are given vasodilators.

Nitrates, either oral or topical, have been used to treat some patients with PPH, although the experience with these agents to date is limited. Direct acting agents, such as hydralazine and diazoxide, may be useful in select patients with marked reactivity, but systemic hypotension has limited their utility. Results with angiotensin converting enzyme inhibitors have been disappointing, and their use is not recommended.

Jones and colleagues[76] first reported using continuous intravenous infusion of prostacyclin in PPH, demonstrating sustained improvement in exercise tolerance with this aggressive approach.[76] Sustained improvement in hemodynamics has been recently demonstrated in a series of PPH patients who were treated with long-term continuous intravenous prostacyclin.[73] The drug is delivered by a portable infusion pump which is connected to a Hickman catheter inserted into the jugular or subclavian vein. Complications have generally been attributable to the drug delivery system and have included thrombosis or infection of the indwelling catheter, pump malfunction, or interruption of the infusion for other reasons. Dose requirements tend to increase over time, suggesting tachyphylaxis, although several patients have maintained responses for periods extending beyond 5 years. This approach may be particularly useful as a bridge to transplantation in seriously ill patients in whom oral vasodilator therapy is either contraindicated or of no demonstrable benefit. Recent experience suggests that prostacyclin may improve survival in New York Heart Association class III and IV patients.[77]

Atrial Septostomy

Patients with PPH in whom the foramen ovale is patent have been reported to live longer than those without a patent foramen ovale.[78] Additionally, patients with Eisenmenger's syndrome due to an atrial septal defect have a better prognosis than PPH patients who have an intact interatrial septum.[79]

Successful palliation of symptoms with a blade balloon atrial septostomy has been reported in patients with advanced pulmonary vascular disease.[80] Recently, Kerstein et al[81] reported improvement with septostomy in 15 patients with syncope and right-sided heart failure. Thus, blade balloon septostomy may serve as adjunct palliative therapy in selected patients with severe PPH and intractable right-sided heart failure. It should be emphasized that this invasive approach is investigational.

Transplantation

Combined heart-lung transplantation has been performed successfully on patients with PPH for nearly a decade.[82] The major limitations to its widespread use include the limited number of centers with the expertise to perform the procedure and care for these patients, and the limited availability of suitable donor organs. Additional problems have included the high incidence (25 to 40 percent) of bronchiolitis obliterans in transplanted lungs, organ rejection, and opportunistic infections.

Recently, single and double lung transplantation has been performed successfully in patients with PPH.[83] Pulmonary artery pressure has fallen, and right ventricular function has improved dramatically in the few patients evaluated to date. Although rejection, infection, and bronchiolitis may occur with lung transplantation as well, it is likely that there should be a greater availability of suitable donor organs for lung transplantation than for combined heart-lung transplantation. Thus, lung transplantation may be the surgical procedure of choice for patients in whom right-sided heart function is not irreversibly impaired. There is no uniform census on the preference of single or double lung transplantation for PPH at present.

Patients with severe right-sided heart failure, hepatomegaly, hyperbilirubinemia, and ascites are not suitable candidates for transplantation since there is an excessively high mortality rate in this group.

The timing of transplantation is controversial and dependent, in part, on the individual patient's wishes. In general, consideration for transplantation is advised for patients who fall into New York Heart Association functional class III or IV who are refractory to medical management.

Prognosis and Natural History

The clinical course of PPH is generally one of inexorable progression toward death. However, natural history studies vary in reporting and in case

ascertainment, and utilize different definitions of survival duration (*eg*, the interval since onset of symptoms or the interval since diagnosis), so that a consensus about the rate of progression of the disease has been difficult to establish.

Among patients who do not undergo heart-lung transplantation, actuarial survival at 1 year is 68 to 77 percent; 2 years, 52 to 58 percent; 3 years, 40 to 56 percent; 4 years, 30 to 43 percent; and 5 years, 22 to 38 percent.[54,70,84] The usual mechanisms of death are right ventricular failure (63 percent), pneumonia (7 percent), and sudden death (7 percent).[54,70]

Despite the overall dismal prognosis, duration of survival ranges up to 10 years or more. Isolated instances of survival up to 24 years have been reported,[85] as have rare cases of apparent regression of the disease.[86]

A variety of indicators appear to have predictive value for short survival.

(1) Higher Pulmonary Vascular Resistance and Pressure: Most studies have found an inverse correlation between the pulmonary hemodynamic abnormality and survival.[54,84,87] Among the 194 patients in the Patient Registry for the Characterization of Primary Pulmonary Hypertension, median survival for those with a mean pulmonary arterial pressure less than 55 mm Hg was 48 months, compared to 12 months for those with mean pulmonary arterial pressure of 85 mm Hg or more.[54]

The implications may be that in these patients, the disease is more advanced or has progressed to a more severe level relatively rapidly (*ie*, by the time of correct diagnosis). The higher pressure imposes a greater workload on the right ventricle, contributing to death from right-sided heart failure, the most common cause of mortality.

Some studies, however, have failed to identify degree of pulmonary hypertension as a predictor of mortality, despite finding a correlation with pulmonary resistance.[88]

(2) Absence of Favorable Response to Vasodilator Therapy: The response to vasodilator therapy has long been recognized as being predictive of survival. There are two potential components to this predictor. First, the ability of the pulmonary vasculature to respond to vasodilator agents may identify patients in a more vasoreactive (earlier) phase of the disease. Thus, those who demonstrate reduced pulmonary vascular resistance with acute administration of vasodilators tend to survive longer, and this may be independent of subsequent treatment status.[89] Second, in addition to the predictive role of vasodilators, there is suggestive evidence that treatment with vasodilators may enhance survival.[34,73] Preliminary data from a 12-week randomized survival study of PPH patients treated with prolonged intravenous prostacyclin also support

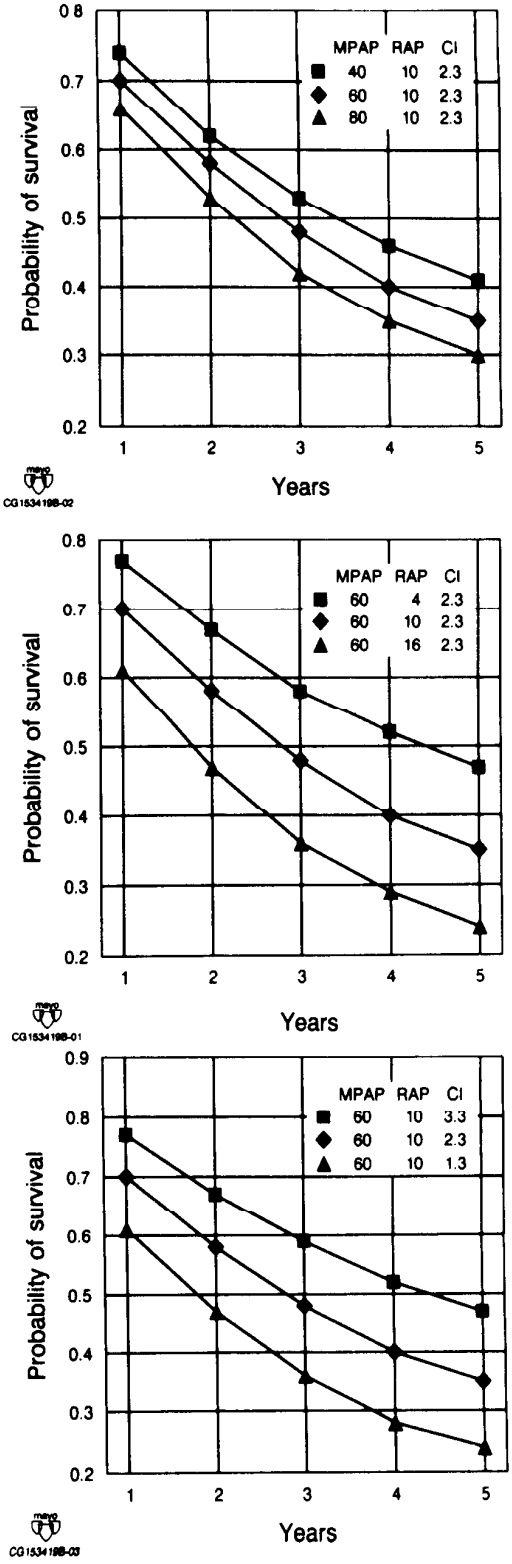

FIGURE 3. Probability of survival for medically treated patients with PPH. Differences in survival probability are depicted based upon variation of baseline mean pulmonary artery pressure (MPAP, mm Hg) (*upper*); right atrial pressure (RAP, mm Hg) (*center*); and cardiac index (CI, L/min/m^2) (*lower*). Adapted from D'Alonzo et al.[54]

this observation.[77]

(3) Worse Functional Classification: Most patients with PPH are symptomatic at the time of diagnosis. Nevertheless, symptoms are presumably a late development in this disease, resulting mainly from end-organ (right ventricular) sequelae. Level of symptomatic deterioriation may be considered a global clinical index of hemodynamic dysfunction. Among symptomatic patients, those exhibiting more symptomatic decompensation have shorter subsequent survival.[89] In the registry, median survival for patients in New York Heart Association class I or II was 58.6 months; class III, 31.5 months; and in class IV, 6 months.[54]

(4) Right Atrial Pressure (RAP) Elevation: Among measurable hemodynamic indices of right ventricular function, mean RAP elevation is highly predictive of survival. Mean RAP greater than 20 mm Hg corresponds to a median survival of 1 month, compared to 46 months survival for patients with mean RAP less than 10 mm Hg.[54]

(5) Depressed Cardiac Output: Decreased cardiac output is associated with severity of PPH. It is caused by both high fixed resistance to blood flow through the pulmonary vasculature and right ventricular failure. Not unexpectedly, reduced cardiac output also correlates with reduced survival.[54,70,87] Cardiac index less than 2.0 L/min/m^2 is associated with a median survival of 17 months; cardiac index of 4.0 L/min/m^2 or more increases median survival to 43 months.[54]

(6) Low Pulmonary Arterial (Mixed Venous) Oxygen Desaturation: Low (less than 63 percent) $S\bar{v}O_2$ predicted a mean 3-year survival of 17 percent, whereas higher $S\bar{v}O_2$ predicted a mean survival of 55 percent at 3 years.[70] The power of this factor is probably derived from its cumulative reflection of poor oxygenation due to reduced capacity, arterial hypoxemia, and low cardiac output.

Based on data obtained from the registry, an equation to predict an individual patient's chances of survival has been developed:[54]

$$P(t) = [H(t)]^{A(x,y,z)}$$

$$H(t) = [0.88 - 0.14t + 0.01t^2]$$

$$A(x,y,z) = e^{(0.007325x + 0.0526y - .3275z)}$$

where:

P(t) = a patient's chances of survival at t years

t = 1, 2, or 3 years

x = mean pulmonary arterial pressure

y = mean right atrial pressure

z = cardiac index

The use of such an equation will be important in assessing appropriateness of treatment modalities, such as lung transplantation, for which survival data can be compared. Examples of survival probability are shown in Figure 3 for three different sets of hemodynamic variables.

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PRIMARY PULMONARY HYPERTENSION: AN OVERVIEW

25

A.Y. Butt and T.W. Higenbottam

25.1 INTRODUCTION

Many new concepts have emerged in this last decade which have improved our understanding of pulmonary vascular disease. Discovery of endothelium-derived nitric oxide (EDNO) [1–3] and endothelins [4], introduction of high dose calcium channel blockers [5,6], continuous infusion of prostacyclin (PGI_2) [7,8] and heart–lung transplantation [9] are some of the landmarks. Primary pulmonary hypertension (PPH), however, is still not fully understood. Its etiology remains unknown and the long-term survival is quite poor as most patients die within 10 years [10,11]. Fortunately, it is an uncommon condition but yet an important one, as it mostly affects young people mainly in their third or fourth decades. Occasionally, children and the elderly also suffer from the disease [12]. In most patients, it follows a progressive course terminating in right ventricular failure [13]. However, there is a small minority of patients, particularly those with well preserved cardiac output (CO), where the disease can regress.

In the USA, the National Institutes of Health (NIH) have established a registry on PPH in which 32 centers around the country have participated. This has provided useful information about the natural history and prognosis of PPH [11,12]. Such a database has been lacking in Europe, but currently an international study on PPH (IPPHS) is being carried out in five European countries. This is an epidemiological survey which is expected to be completed in 1995 and is designed to study the natural history and risk factors for PPH. So far centers from France, UK, Belgium, Netherlands and Switzerland have participated in the survey, and patients have been included. In this study, emphasis has been placed on any relevant prior drug history, particularly anorexic drugs which are widely used in continental Europe.

In order to diagnose pulmonary hypertension, it is mandatory to perform right heart catheterization and measure pulmonary artery pressure (PAP) directly. (For a description of diagnostic catheter technique, see Chapter 5.) A normal systolic PAP at sea level for a CO of 5 l/minute is approximately 20 mmHg and diastolic pressure is 12 mmHg. A mean PAP in excess of 25 mmHg at rest and 30 mmHg on exercise indicates pulmonary hypertension but not the cause [14]. In situ-

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ations with elevated PAP it is important to look for an underlying cause such as pulmonary embolism, intracardiac shunts, left heart disease, chronic lung disease and hypoventilation. A diagnosis of PPH is, therefore, made by exclusion.

25.2 PATHOPHYSIOLOGY

The low resistance pulmonary vasculature can react differently to systemic arteries and in susceptible individuals may have an augmented response to stimuli such as hypoxia, increased blood flow and various pharmacological and dietary substances, leading to pulmonary vasoconstriction and development of pulmonary hypertension. Much attention has been paid to the role of endothelium in the pathogenesis of PPH as histological studies have demonstrated intimal thickening as a common finding [15,16]. The role of endothelium in the release of various prostanoid and non-prostanoid factors is well recognized. Some of these substances, such as EDNO and PGI_2, are potent vasodilators [17,18], and may have an additive effect on each other. EDNO causes a rise in cyclic 3,5-guanosine monophosphate (cGMP) [19] while PGI_2 promotes a rise in cyclic 3,5-adenosine monophosphate (cAMP) [20] in the vascular smooth muscle cells, both leading to vascular relaxation (see Chapters 8 and 9).

Endothelium may also produce various constricting substances, called endothelium-derived constricting factors (EDCF); endothelin-1 (ET-1) being probably the most important [4]. In physiological states, there is a fine balance between these substances in order to sustain a normal vascular tone. However, in endothelial dysfunction release of EDNO and PGI_2 may be impaired [21,22], thus tilting the balance in favor of EDCF causing a rise in pulmonary vascular tone. Alternatively ET-1 or thromboxane [22,23] may be released in excessive amounts leading to pulmonary vasoconstriction.

Antiphospholipid antibodies or anticardiolipin antibodies (ACA) [24] are found in systemic lupus erythematosis (SLE) and are associated with thrombotic complications. Occasionally, these antibodies which are IgG or IgM [25] in nature may also be found in the absence of any clinical SLE. There is some evidence that these antibodies may interfere with the formation of PGI_2 resulting in local deficiency of PGI_2 [26–28].

Platelets may also have a role in PPH as they release various important vasoactive factors, particularly serotonin (5-HT). Spontaneous pulmonary hypertension has been seen in the fawn-hooded rat which has abnormal platelet friability [29]. In experimental studies *in vitro* we have demonstrated that serotonin is a potent vasoconstrictor of human pulmonary arteries and, therefore, might have a role in the pathophysiology of PPH.

Genetic predisposition may explain familial types of PPH. Approximately 7% of patients from the NIH registry had familial disease. Familial tendency towards pulmonary hypertension has also been observed in patients exposed to high altitude and various chemicals, such as aminorex fumarate [30], monocrotaline [31], or Spanish toxic rapeseed oil [32].

25.3 DIAGNOSIS

25.3.1 SYMPTOMS

There are three main symptoms, that is, dyspnea, chest pain and syncope [12,33,34]. The disease has an insidious onset and the often mild symptoms may go unnoticed by the patients. It is not uncommon that a delay of up to 2 years may occur before a diagnosis can be made [12]; therefore, it is necessary that clinicians should look for any signs of pulmonary hypertension in patients where symptoms are unexplained. Dyspnea is secondary to low cardiac output and poor metabolic gas exchange, which leads to hypoxia and reflex hyperpnea. This can be graded as I to IV according to the New York Heart

Association (NYHA) criteria and reflects the severity of pulmonary hypertension and also prognosis. Chest pains are angina-like and are due to right ventricular hypertrophy as coronary angiography is normal. Syncope, usually on exercise, is a sinister feature and reflects severe right ventricular dysfunction. Presyncopal symptoms on exercise may occur in less severe disease. Syncope at rest is uncommon and is usually due to a cardiac arrythmia. Other symptoms, such as tiredness, ascites and peripheral edema, may occur in PPH. Features of autoimmune disease, such as skin rashes, Raynaud's phenomenon, arthropathy, jaundice due to chronic active hepatitis or primary biliary cirrhosis and thrombocytopenia due to autoimmune destruction of platelets, may also be present. It is essential that any history of an underlying disease, such as valvular heart disease, myocardial disease, chronic lung disease and thromboembolic disease, are excluded. History of anorexic drugs, antidepressants and the contraceptive pill is particularly important. Onset of symptoms may be found in association with pregnancy [35], going to high altitudes, and use of fenfluramine [36,37] or contraceptive pills [38,39].

25.3.2 SIGNS

At the time of presentation, patients may be greatly disabled and dyspneic at rest. Both peripheral and central cyanosis may be present. Peripheral perfusion is quite low, in most cases with cold extremities. Tachycardia along with a low volume pulse may be present. Jugular venous pressure is usually raised and venous 'a' and 'v' waves may be present [40]. Loud pulmonary component of the second heart sound (P2), best audible at the pulmonary area, may also be palpable. Cardiac impulse is usually tapping in nature along with the presence of left parasternal heave. Right ventricular third and/or fourth heart sounds are occasionally heard. A systolic murmur is a common feature and is mostly due to tricuspid regurgitation, but may also be due to flow across the pulmonary valve. A diastolic murmur due to pulmonary regurgitation is occasionally present. Peripheral leg edema and ascites are relatively uncommon and may indicate severe disease. PPH is associated with various autoimmune diseases [41,42]; therefore, features of scleroderma, rheumatoid disease and SLE may be present in the absence of any parenchymal lung disease.

25.3.3 INVESTIGATIONS

Blood count occasionally shows low platelet count, the cause of which is not clear, but we have seen one patient with PPH showing severe autoimmune thrombocytopenia which responded to immunosuppressive therapy. Raised erythrocyte sedimentation rate may suggest an underlying connective tissue disease or a vasculitic process. However, the presence of antineutrophil cytoplasmic antibodies (ANCA) is a more specific indicator of vasculitis. Renal function may be disturbed, especially in advanced disease. Liver function may also be deranged; this is commonly due to hepatic congestion, but may also be due to an associated autoimmune liver disease. Antinuclear factor may be present in nearly one-third of the patients in the absence of lupus [10,41]. Antiphospholipid antibodies are occasionally present and may contribute to thromboembolic events. Antithrombin III and protein C deficiency should also be sought.

Electrocardiogram (ECG) and chest radiograph (CXR) are abnormal in nearly 90% of cases. ECG typically shows right axis deviation and evidence of right ventricular hypertrophy (Fig. 25.1). Presence of right ventricular strain is suggestive of severe pulmonary hypertension and may have some prognostic significance [42]. The most common finding on CXR is enlargement of proximal pulmonary arteries, sometimes associated with peripheral pruning (Fig. 25.2(a)). The heart may be enlarged in more severe disease (Fig. 25.2(b)).

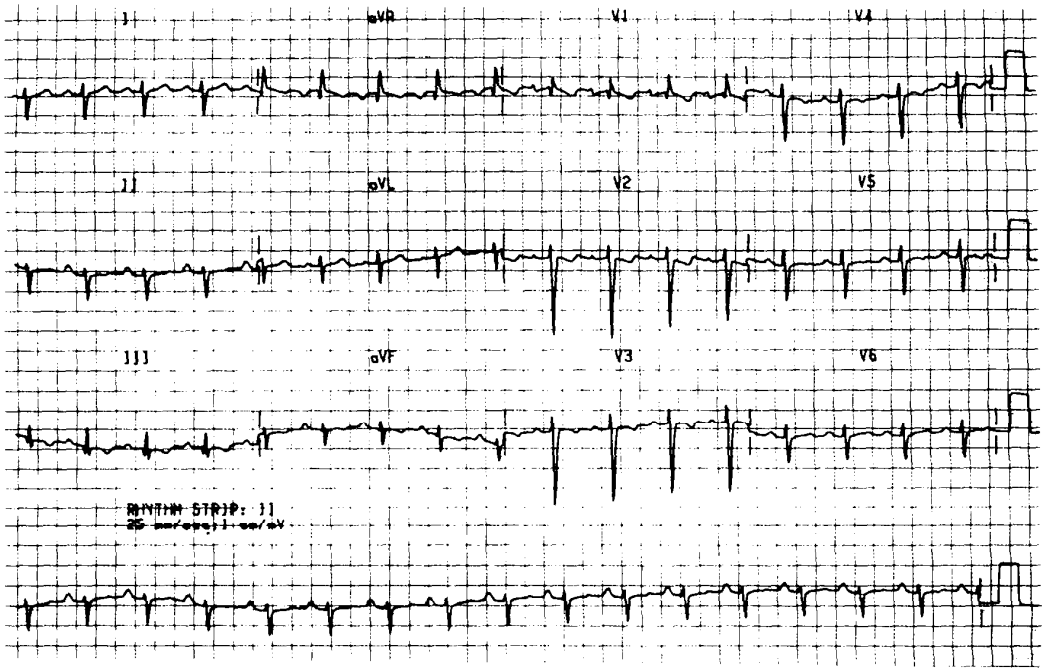

Fig. 25.1 Electrocardiogram from a patient with pulmonary hypertension showing right axis deviation and evidence of right ventricular hypertrophy.

Dilatation of the right atrium may also be seen on the radiograph. Cross-sectional echocardiograph classically shows dilatation of the right-sided chambers in conjunction with right ventricular and septal hypertrophy [43] (Plate 13). Paradoxical septal motion is occasionally seen. PAP may be calculated indirectly provided tricuspid regurgitation (TR) is present. By using Doppler, the velocity of the TR jet can be measured and PAP can be calculated (see Chapter 4). Ventilation and perfusion (VQ) scan of the lung excludes the presence of pulmonary emboli [44–46]. In PPH, perfusion may be either normal or patchy while in pulmonary emboli segmental or subsegmental VQ mismatches are seen. In patients where proximal thrombus is suspected, pulmonary angiogram is undertaken (Fig. 25.3). Spiral computerized tomogram (CT) [47] and magnetic resonance imaging (MRI) of the chest are emerging as non-invasive methods to visualize proximal clots (Fig. 25.4). Multiple gated acquisition (MUGA) scan may be used to detect ejection fraction; it may also show dilatation of the right ventricle. Arterial blood gases usually show hypoxia and hypocapnia, and lung volume studies generally show a restrictive pattern with lower than predicted values of forced vital capacity (FVC), forced expiratory volumes and total lung capacity. Gas diffusion capacity measured as transfer factor is also impaired [12] without the presence of interstitial lung disease.

25.3.4 RIGHT HEART CATHETERIZATION

It is essential to make a direct measurement of PAP in order to diagnose pulmonary hypertension. Right heart catheterization (RHC) is

Fig. 25.2 Chest radiograph from patients with PPH showing dilatation of the proximal pulmonary artery (a) associated with enlargement of the heart (b). Note: central line *in situ* is used for the administration of long-term prostacyclin infusion (b).

Fig. 25.3 Pulmonary angiogram of a patient with thromboembolic pulmonary hypertension showing an organized thrombus in the left main pulmonary artery causing narrowing of the lumen. Patient subsequently underwent thromboendarterectomy. (By courtesy of Dr. C.D.R. Flower and Mr J. Wallwork.)

performed using a Swan–Ganz catheter [48], which is inserted through the internal jugular route and is positioned into a descending branch of the pulmonary artery. PAP, right atrial pressure (RAP), CO and pulmonary artery wedge pressure (PWP) are measured. Blood samples from the pulmonary artery, as well as the radial artery, are taken for gas analysis. Pulmonary vascular resistance (PVR) can be calculated using this formula:

$$\text{PVR (Wood units)} = \frac{\text{PAP} - \text{PWP}}{\text{CO}}$$

It is desirable to make these measurements at baseline and after a vasodilator challenge using a short-acting vasodilator. We use intravenous PGI_2 which is a naturally occurring arachidonic acid metabolite. It is a potent vasodilator with a half-life of less than 5

Fig. 25.4 Computerized tomography (CT) of the chest with spiral acquisition showing organized thrombus in the right main artery (arrow). Note the presence of calcium in the thrombus.

minutes *in vivo* and, therefore, is an ideal agent for a diagnostic study [49]. It is commenced at 2 ng/kg/min and increased in a stepwise fashion by 2 ng/kg/min after every 10 minutes. Before increasing the dose all the measurements are repeated. PGI_2 infusion is continued until there is a 20% or more drop in PVR or the patient gets side-effects, such as nausea, headache or hypotension. RHC is mandatory, not only to confirm the diagnosis, but also to establish a prognostic status of the patient. Presence of right ventricular dysfunction, low pulmonary artery oxygen saturation (SvO_2) and functional class NYHA, grade III to IV are poor prognostic indicators. Using data from the NIH registry, D'Alonzo *et al.* [11] have devised an equation which may be used to determine prognosis for an individual patient [11]:

$$A = e^{(0.007325x) + (0.0526y) - (0.3275z)}$$

where 'x' denotes mean PAP, 'y' is RAP and 'z' is cardiac index (CI) determined at the time of initial catheterization. The probability (P) of surviving 1, 2 and 3 years can then be calculated in per cent by using the following formulae:

$P(1) = .75^A$
$P(2) = .65^A$
$P(3) = .55^A$

Mean PAP of 85 mmHg or more and cardiac index of 1.95 l/min/m^2 or less were associated with poor prognosis. An increase in right atrial pressure from 10 mmHg to 20 mmHg or more was associated with a drop in the median period from 46 months to only 1 month. Fuster *et al.* [10], in a retrospective analysis, have found an SvO_2 of less than 63% was associated with 3-year survival chance of only 17%, while SvO_2 of more than 63% was associated with 55% chance of survival over the same period. We have also found functional class of prognostic significance, patients categorized into NYHA grade III–IV have a poorer prognosis than patients in grade I–II.

25.4 TREATMENT

Therapeutic options are limited in PPH as the underlying disease is complex and the etiology remains unknown. The main objectives of treatment are to lower PVR and prevent thromboembolic complications. Therefore, anticoagulants and vasodilators are the mainstay of treatment. Long-term anticoagulant therapy has been found to be associated with improved survival [10]. A number of vasodilators are available, but they may not be as effective on pulmonary arteries as they are on systemic vessels and, therefore, cannot be used at will. Hydralazine [54] and captopril [55] have been used, but the long-term results are not favorable. Calcium channel blockers are currently in vogue in the treatment of mild to moderate PPH [5,6,52]. Both nifedipine and diltiazem have been tested as pulmonary vasodilators. By using high dose calcium channel blockers, that is, 240 mg/day of nifedipine and 720 mg/day of diltiazem, Rich and Brundage [5] have not

only shown symptomatic and hemodynamic improvement, but also demonstrated regression of right ventricular hypertrophy and improvement in right axis deviation in patients with PPH. In 1992, using the similar regime of Ca^{2+} channel blockers, they further demonstrated a marked improvement in 5-year survival [6] in the group who showed significant pulmonary vasodilatory responsiveness to acute challenge [53,54]. (For a review of vasodilators in PPH, see Chapter 27.)

However, in severe PPH with impaired cardiac function and low SvO_2, Ca^{2+} channel blockers may be detrimental because of their negative inotropic effect and should be used with extreme caution. A vasodilator without any myocardial suppressant effect is required in such a situation and prostacyclin (PGI_2) may fulfil that role [59]. It is a potent vasodilator, but is highly unstable and cannot be taken orally. It is dissolved in a sodium glycine buffer and has to be administered as a continuous infusion through an indwelling tunneled central line. It is highly expensive and has to be self-administered; therefore, major commitment is required from the patients as well as their carers. This form of treatment is reserved only for those patients who otherwise would have a poor quality of life and a poor chance of survival. We, along with others, have shown that continuous PGI_2 infusion improves well-being as well as mortality in severe PPH [7,8,56–59]. Rubin *et al.* [8], in a randomized trial, have demonstrated significant hemodynamic improvement during a repeat catheter study after 8 weeks of treatment with PGI_2. However, there are indications that in severe pulmonary hypertension, PGI_2 may help not only those patients showing pulmonary vasodilatation to acute challenge, but also those who do not [60], suggesting that PGI_2 may have additional actions such as rehabilitation of vascular endothelium, antithrombotic effect and remodeling of the pulmonary vasculature.

Iloprost is a synthetic analogue of prostacyclin which is not yet commercially available. It is more stable, has a slightly longer half-life (approximately 13 minutes), can be stored at room temperature and does not have to be dissolved in glycine buffer. It has also been shown to cause pulmonary vasodilatation [61] and improves the well-being of patients with pulmonary hypertension [62].

Another treatment for PPH which has come into use during the last few years is heart–lung transplantation (HLT) [9]; it is reserved for patients with severe disease, particularly those not responding to PGI_2. Patients' age and psychosocial stability and absence of any systemic disorder are taken into account. Single lung transplantation for PPH [63,64] is at an experimental stage and has been attempted at some centers. (For a review of transplantation in PPH, see Chapter 28.)

Inhaled nitric oxide (NO) has a potential in the treatment of pulmonary hypertension once a safe delivery apparatus is available for long-term use. This is a highly labile gas with a half-life of only a few seconds. Once inhaled in dilutions of 40 ppm in air it can cause pulmonary vasodilatation by approaching the vascular smooth muscle cells abluminally [65]. It is quickly inactivated on contact with hemoglobin and there is little chance of systemic ill-effects.

Phosphodiesterase inhibitors, such as enoximone, have inotropic as well as pulmonary vasodilatory activities [67–70], and may play a useful role in the treatment of selected patients with severe PPH where conventional therapy is not effective.

25.5 SUMMARY

PPH is a serious disease which affects young people but, fortunately, is uncommon. Its etiology is unknown, but endothelial dysfunction may play an important role in its pathogenesis. Right heart catheterization (RHC) and exclusion of any secondary cause of pulmonary hypertension are essential. RHC confirms the diagnosis and gives prognostic information. Patients with mild to moderate

disease are treated with anticoagulant along with high dose calcium channel blockers if they demonstrate pulmonary vasodilatory responsiveness to an acute vasodilator challenge. Patients with severe PPH are considered for HLT and may be treated with continuous infusion of prostacyclin during the interim period. Inhaled NO may become a treatment in future. Further studies are required to understand the complex disease process before a more successful treatment becomes available for a disease which has a bleak prognosis.

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Primary Pulmonary Hypertension

A National Prospective Study

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A national registry was begun in 1981 to collect data from 32 centers on patients diagnosed by uniform criteria as having primary pulmonary hypertension. Entered into the registry were 187 patients with a mean age (± SD) of 36 ± 15 years (range, 1 to 81), and a female-to-male ratio of 1.7:1 overall. The mean interval from onset of symptoms to diagnosis was 2 years. The most frequent presenting symptoms included dyspnea (60%), fatigue (19%), and syncope (or near syncope) (13%). Raynaud phenomenon was present in 10% (95% of whom were female) and a positive antinuclear antibody test, in 29% (69% female). Pulmonary function studies showed mild restriction (forced vital capacity [FVC], 82% of predicted) with a reduced diffusing capacity for carbon monoxide (D_{LCO}), and hypoxemia with hypocapnia. The mean (± SD) right atrial pressure was 9.7 ± 6 mm Hg; mean pulmonary artery pressure, 60 ± 18 mm Hg; cardiac index, 2.3 ± 0.9 L/min·m²; and pulmonary vascular resistance index, 26 ± 14 mm Hg/L/min·m² for the group. Although no deaths or sustained morbid events occurred during the diagnostic evaluation of the patients, the typically long interval from initial symptoms to diagnosis emphasizes the need to develop strategies to make the diagnosis earlier.

[MeSH terms: alkalosis, respiratory; anoxemia; antinuclear factors; carbon monoxide; dyspnea; fatigue; hemodynamics; hypertension, pulmonary; Raynaud's disease; sex factors; syncope; vascular resistance; vital capacity. Other indexing terms: cardiac index; diffusing capacity; hypocapnia; pulmonary artery pressure; right atrial pressure]

THE RECOGNITION OF pulmonary vascular disease as a primary cause of pulmonary hypertension was first attributed to Romberg (1) in 1891 in a case report of a patient with unexplained pulmonary hypertension. In 1951, Dresdale and associates (2) collected data on 39 patients with unexplained pulmonary hypertension and coined the term *primary pulmonary hypertension* to describe the condition, a term that is still used today. Wood (3) described the clinical features of this disease in a series of 17 patients in 1959, and by 1971 more than 600 cases had been reported. Although the basic clinical presentation has been well documented, many questions remain as to the epidemiology, pathogenesis, natural history, and treatment of primary pulmonary hypertension. Until recently, no single institution has been able to accumulate data on a sufficient number of patients to address many of these issues.

In 1973 the World Health Organization met to review the current state of knowledge regarding the epidemiologic, clinical, and pathologic features of primary pulmonary hypertension and proposed that consideration be given to establishing a multicenter collaborative study involving these patients (4). In 1981 the Division of Lung Disease of the National Heart, Lung, and Blood Institute, National Institutes of Health, initiated the Patient Registry for the Characterization of Primary Pulmonary Hypertension. The goals of the registry were to obtain and evaluate data on the natural history, cause pathogenesis, and treatment of primary pulmonary hypertension, with the hope that new strategies might evolve to allow early detection of the disease and the development of a rational therapeutic approach. We review baseline data from 187 patients with primary pulmonary hypertension who have been entered in the registry.

Methods

Thirty-two medical centers (*see* Appendix) were to report data on standardized reporting forms from patients with primary pulmonary hypertension who were seen between 1 July 1981 and 30 September 1985. Pulmonary hypertension was defined as the presence of a mean pulmonary arterial pressure of greater than 25 mm Hg at rest or 30 mm Hg with exercise at catheterization.

Because no clinical feature or laboratory variable is recognized as pathognomonic for primary pulmonary hypertension, the diagnosis was accepted only after the following secondary causes for pulmonary hypertension were excluded: pulmonary hypertension within the first year of life, and congenital abnormalities of the lungs, thorax, and diaphragm; congenital or acquired valvular or myocardial disease; pulmonary thromboembolic disease as evidenced either by lung perfusion scan (other than normal or low probability) or positive pulmonary angiogram, a diagnosis of sickle cell anemia, or a history of intravenous drug abuse; obstructive lung disease as manifested by hypoxemia and reduced flow rates (forced expiratory volume in 1 second/forced vital capacity > 2 SD from predicted norm); interstitial lung disease as evidenced by a reduction in total lung capacity of more than 2 SD from the predicted norm associated with pulmonary infiltrates on chest roentgenogram; arterial hypoxemia associated with hypercapnia; collagen vascular disease as classically defined (5); parasitic disease affecting the lungs; pulmonary artery or valve stenosis as documented by pulmonary artery pressure gradients during right heart catheteriza-

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tion, and pulmonary venous hypertension with pulmonary capillary wedge pressures in excess of 12 mm Hg. Cases in which doubt existed as to the primary nature of the pulmonary hypertension were reviewed by the steering committee and ruled by consensus as either meeting or not meeting criteria.

Patients judged to have satisfied the above criteria were also required to have the following data supporting the diagnosis of primary pulmonary hypertension for their cases to be classified as primary pulmonary hypertension: demographic data including age, sex, race, height, and weight; a chest radiograph, pulmonary function tests with arterial blood gas pressures measured during the breathing of room air, a lung perfusion scan or a pulmonary angiogram; evaluation of an intracardiac left-to-right shunt, either by angiogram, hydrogen curve, indicator dilution test, or oximetry; and baseline hemodynamic variables including right atrial pressure, pulmonary systolic, diastolic, and mean pressures, pulmonary capillary wedge pressure, systemic systolic and diastolic pressures, and cardiac output. Data on history, physical examination, and other laboratory findings were also collected.

STATISTICAL ANALYSIS

Statistical methods used to characterize the variables were descriptive (means, standard deviations, product moment correlation coefficients). Methods used to evaluate differences among groups included *t*-tests, chi-square tests, and, where appropriate, the Mantel-Haenszel test. The Cochran-Armitage test was used to test for trend when comparing several proportions. Values obtained for pulmonary function tests and arterial blood gases were standardized to previously published norms (6–9) and converted to the percent predicted value for that test. The *p* values reported are two-sided and nominal (not adjusted for multiple comparisons).

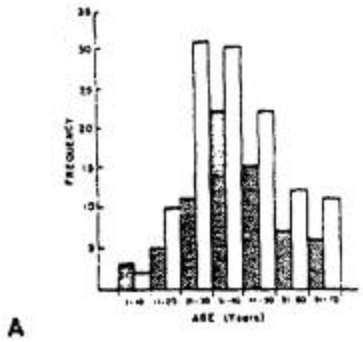
Results

DEMOGRAPHIC CHARACTERISTICS

The age and sex distribution of 187 patients with primary pulmonary hypertension entered into the registry are shown in Figure 1A. The mean age of patients enrolled was 36.4 years and was similar for male and female patients. Although the age distribution of patients with this disease showed the highest frequency in the third decade for female patients, and the fourth decade for male patients, 9% of the patients were more than 60 years of age. The female-to-male ratio was 1.7:1 and was relatively constant for each decade. Female patients tended to have more severe symptoms at presentation, with 75% in functional class III or IV (according to New York Heart Association criteria) compared with 64% for male patients ($p = 0.08$). The distribution of patients by race was similar to that of the general population, with 12.3% black and 2.3% Hispanic. Interestingly, there was a greater female-to-male preponderance in the black population (4.3:1), with a similar age distribution as the white population.

SYMPTOMS

Dyspnea was by far the commonest initial symptom, occurring in 60% of all patients. Ninety-eight percent, however, had dyspnea by the time they were enrolled at the clinical centers. Fatigue (19%), chest pain (7%), near syncope (5%), syncope (8%), leg edema (3%), and palpitations (5%) were less common initial symptoms. However, fatigue was present in 73% of the patients, chest pain in 47%, near syncope in 41%, syncope in 36%, edema in 37%, and palpitations in 33%, of the patients by the time they were enrolled. Twenty-nine percent of the patients had mild symptoms (functional class II) at the time of entry into the registry. When compared with the more symptomatic patients (functional class III and IV), these patients were less likely to have fatigue (58% compared with 79%; $p = 0.01$) or peripheral edema (23% compared with 41%; $p = 0.06$).



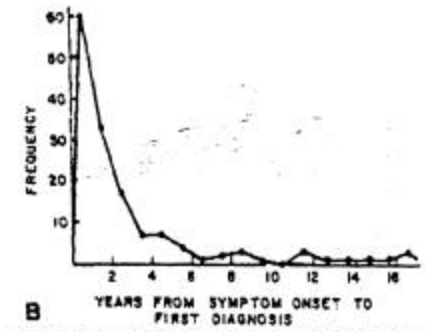


Figure 1. Distribution of patients with pulmonary embolism plotted according to age based on sex (*A*) and according to onset of symptoms for both sexes (*B*). The disease was most prevalent in age groups in the third and fourth decades, but the female-to-male ratio of 1.7 to 1 was not significantly different among decades. The mean time to onset of initial symptoms, 2.03 years (median, 1.27), was similar for both male (*shaded bars*) and female (*open bars*) patients.

The time from onset of the first symptom until the diagnosis of primary pulmonary hypertension was made is shown in Figure 1B. The mean time from onset to diagnosis was 2.03 ± 4.9 years (median, 1.27) and was similar for male and female patients. Although more than 90% of the patients had their illness diagnosed within 3 years of presenting symptom onset, on occasion patients stated that their symptoms had been present for up to 20

years before the diagnosis was made. Only 10% of the patients reported symptoms of Raynaud phenomena, which occurred almost entirely (95%) in the female patients.

MEDICAL AND FAMILY HISTORY

Forty-five percent of the patients were previous or current cigarette smokers, and only 5% had histories of appetite suppressant drug use. Fifty-four percent of the female patients had taken oral contraceptives at some time. There were 2.3 live births per female patient in the registry. None of these frequencies appear to differ dramatically from those found in the general population. There were 12 cases (6%) of familial pulmonary hypertension (disease affecting a first-order blood relative), 7 in men and 5 in women. Patients who had positive family histories were usually diagnosed sooner after the onset of symptoms than were the other registry patients (0.68 compared with 2.55 years; $p = 0.0002$). There were no differences, however, in their ages or hemodynamic findings.

PHYSICAL FINDINGS

The physical findings of patients with primary pulmonary hypertension were typical of any patient with pulmonary hypertension. An increase in the pulmonic component of the second heart sound (P_2) was reported in 91%, a right-sided third heart sound (S_3), in 23%, and a right-sided fourth heart sound (S_4), in 38%. The presence of an S_3 was associated with elevated right atrial pressure (11 compared with 9 mm Hg; $p < 0.001$) and a reduced cardiac index (1.8 compared with 2.4 L/min·m^2; $p < 0.0001$). Tricuspid regurgitation was noted in 40% and pulmonic insufficiency, in 13%. The presence of tricuspid regurgitation was also associated with increased right atrial pressure (12 compared with 8 mm Hg; $p < 0.0001$) and a reduced cardiac index (1.77 compared with 2.56 L/min·m^2; $p < 0.001$), whereas the presence of pulmonic insufficiency was associated with a higher mean pulmonary artery pressure (70 compared with 59 mm Hg; $p < 0.03$). Cyanosis was reported in 20%, and peripheral edema, in 32%.

LABORATORY FINDINGS

The chest radiographs, which were subjectively graded at each center, showed the typical constellation of changes associated with pulmonary hypertension—namely, prominence of the main pulmonary artery (90%), enlarged hilar vessels (80%), and decreased peripheral vessels (51%). The presence of all three abnormalities (42%) was associated with a higher mean pulmonary artery pressure (66 compared with 53 mm Hg; $p < 0.001$) and lower cardiac index (2.0 compared with 2.4 L/min·m^2, $p < 0.004$). Interestingly, the chest radiograph was reported to be normal in 6% of the patients.

The electrocardiogram showed right axis deviation in 79%, right ventricular hypertrophy in 87%, and right ventricular strain in 74%. All patients had an underlying sinus rhythm. The echocardiogram (*M*-mode) showed a normal to small left ventricular end-diastolic internal dimension in all patients and right ventricular enlargement in 75%. The calculated pulmonary vascular resistance index correlated inversely with left ventricular end-diastolic dimension ($r = 0.47$, $p < 0.001$) but not with right ventricular end-diastolic dimension. Paradoxic septal motion was described in 59% of the patients and partial systolic closure of the pulmonary valve, in 60%.

Results of an antinuclear antibody test were positive in 29% of the patients, with titers ranging from 1:10 to 1:10 000 (geometric mean, 1:103), although the antigen substrates used were not uniform among centers. There was a female-to-male ratio of 1.4:1 among those reported with a positive result. The lung perfusion scan was normal in 42% and characterized as abnormal in 58% (Table 1). Of the patients who had abnormal scintigrams, only one was reported as having a high probability of pulmonary embolism, and that patient had a normal pulmonary angiogram. Seventy-seven percent of the abnormalities were described as a diffuse patchy pattern; 7%, as single defects; and 12%, as multiple discrete defects. There was no relationship between the hemodynamic findings and the pattern of perfusion as shown by lung scan.

PULMONARY FUNCTION

Selected variables of pulmonary function are presented in Table 2 and Figure 2. Airways obstruction could not be shown, but there was a mild, albeit significant, reduction in total lung capacity in the female patients (mean, 89% of predicted; $p < 0.05$) and in forced vital capacity (FVC) for both male and female patients (mean, 82% of predicted; $p < 0.01$). Although there was wide scatter, the diffusing capacity for carbon monoxide ($D_{L_{CO}}$) measured significantly less than that predicted (mean, 69% of predicted; $p < 0.001$). Hypoxemia and hypocapnia were almost an invariable finding. The arterial oxygen content correlated significantly with mixed venous oxygen content ($r = 0.48$; $p < 0.001$).

HEMODYNAMIC FINDINGS

Hemodynamic variables in patients at the time of catheterization at the clinical centers are summarized in Table 2 and shown in Figure 3. The patients had severe pulmonary hypertension with a threefold increase in mean pulmonary artery pressure (60 ± 18 mm Hg; range, 28 to 127), mild-to-moderate elevation in right atrial pressures (9 ± 6 mm Hg; range, 0 to 29) with normal pulmonary capillary wedge pressures, and mildly reduced cardiac indexes (2.27 ± 0.9 L/min·m^2; range, 0.8 to 7.9). Female patients differed significantly from male patients only with respect to resting heart rates, with the female patients having a faster rate by an average of 7 beats/min ($p = 0.009$).

Correlations between hemodynamic findings and severity of symptoms were also investigated. Patients with more severe symptoms (functional class III and IV) had higher mean pulmonary artery pressures (62 compared with 56 mm Hg; $p = 0.06$), higher right atrial pressures (11 compared with 7 mm Hg; $p = 0.0001$), and lower

cardiac indexes (2.06 compared with 2.71 L/min·m²; $p = 0.0003$) than did their less symptomatic counterparts (functional class II). In contrast, we were unable to find differences in hemodynamic values among patients when they were analyzed according to duration of symptoms. Because young women have often been described as the group most severely afflicted by primary pulmonary hypertension, we compared values in female patients from the ages of 15 to 34 years with those in the men and the women aged 35 or more. No significant differences were found between these groups based on functional class or hemodynamic values.

ADVERSE CONSEQUENCES

None of the 163 patients who had lung perfusion scans reported any adverse complication. Only one adverse reaction (transient hypotension) occurred among the 50 patients reported to have had pulmonary angiography. Of the 187 patients who had cardiac catheterization, 10 reported adverse reactions from the catheterization (not including drug testing). Four had adverse effects that appeared unrelated to the presence of pulmonary hypertension—namely, inadvertent arterial puncture, oversedation, and pneumothorax (in 1 patient). Six patients had adverse effects that were probably related to the underlying pulmonary hypertension, with five episodes of transient hypotension and one of hemoptysis after an angiogram. Fortunately, there were no deaths or sustained morbidity associated with any of these procedures.

Discussion

A major distinction between this study of primary pulmonary hypertension and others, with the exception of the large number of patients enrolled, is its prospective nature compared with previous retrospective studies. The large collection of data from patients with primary pulmonary hypertension who have been enrolled in this registry has allowed better characterization of the disease than ever before. The data have shown that a long symptomatic period has preceded the diagnosis, which likely accounts for the advanced manifestations of pulmonary hypertension at the time of diagnosis. The data have also shown that untoward events from the work-up, including catheterization, were uncommon at the participating centers.

The criteria for patient enrollment into the registry were established in an attempt to obtain as uniform a group of patients as possible without excluding actual cases. Most exclusionary criteria were objectively determined and straightforward. The finding of a ventilation-perfusion lung scan showing normal or low probability for pulmonary emboli has correlated with normal pulmonary angiograms in patients with primary pulmonary hypertension (12, 13) and was thus deemed sufficient to rule out pulmonary embolic disease. Underlying lung disease presents a more difficult issue. Because hypoxemia is the predominant cause of pulmonary hypertension in obstructive lung disease (14), this condition was required to be present, in addition to decreased flow rates, before the pulmonary hypertension was attributed to the lung disease. Pulmonary hypertension caused by restrictive lung disease results primarily from the underlying infiltrative or destructive parenchymal process (14), and thus, diffuse abnormalities shown on the chest roentgenogram were required in addition to a decrease in lung volumes to form exclusion criteria for these patients. Coexistent collagen vascular disease was diagnosed if the patient met well-defined criteria, because the presence of isolated abnormal serologic studies was not deemed sufficient (5).

One common feature in patients with primary pulmonary hypertension is that by the time the diagnosis is made, the patients have clinical and hemodynamic

Table 1. Correlation Between Patterns* of Abnormalities as Detected by Lung Perfusion Scans and Estimated Probability of Pulmonary Embolism†

Patterns	Estimated Probability			
	High	Low	Indeterminate	Total
	n			
Patchy	0	71	1	72
Single defect	0	7	0	7
Multiple discrete defects	1	8	2	11
Not specified	0	3	1	4

* Based on a total of 94 abnormal scintigrams; total number of normal scintigrams = 69.

Table 2. Pulmonary Function Variables and Hemodynamic Findings at Entry into Registry*

	Males	Females
Total lung capacity, *% predicted*†	95 ± 16	89 ± 17
FVC, *% predicted*‡	86 ± 19	79 ± 19
FEV_1, *% predicted*‡	86 ± 19	83 ± 17
FEV_1/FVC	78 ± 10	82 ± 9
D_{LCO}, *% predicted*§	62 ± 25	73 ± 24
Arterial Po_2, *mm Hg*‖	70 ± 13	72 ± 16
Arterial Pco_2, *mm Hg*‖	30 ± 6	31 ± 5
Heart rate, *beats/min*	82.2 ± 14.7	89.1 ± 19.1
Right atrial pressure, *mm Hg*	10.4 ± 6.3	9.3 ± 6.2
Pulmonary artery pressure, *mm Hg*		
Systolic	90.4 ± 27.2	91.7 ± 23.0
Diastolic	43.2 ± 16.8	43.3 ± 14.1
Mean	60.7 ± 19.7	60.3 ± 16.5
Pulmonary capillary wedge pressure, *mm Hg*	8.69 ± 3.9	7.94 ± 3.7
Systemic arterial pressure, *mm Hg*		
Systolic	120.7 ± 19.4	121.5 ± 18.0
Diastolic	75.2 ± 12.1	73.3 ± 11.9
Mean	90.6 ± 15.3	91.9 ± 13.6
Cardiac index, *L/min·m²*	2.35 ± 1.0	2.21 ± 0.9
Pulmonary vascular resistance index, *mm Hg/L/min·m²*	23.87 ± 11.2	27.69 ± 15.9
Systemic vascular resistance index, *mm Hg/L/min·m²*	37.89 ± 12.4	43.45 ± 17.1
Stroke volume index, *mL/beat·m²*	28.92 ± 11.9	25.89 ± 11.1

* All values are expressed as means ± SD. FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, D_{LCO} = diffusing capacity of the lungs for carbon monoxide.

† Calculated according to methods described by Goldman and Becklake (7).

‡ Calculated according to methods described by Morris and colleagues (8).

§ Calculated according to methods described by Bradley and colleagues (11).

‖ Pressures in patients seen in centers at high altitude (Denver, Colorado, and Salt Lake City, Utah) are not included in calculations of the mean.

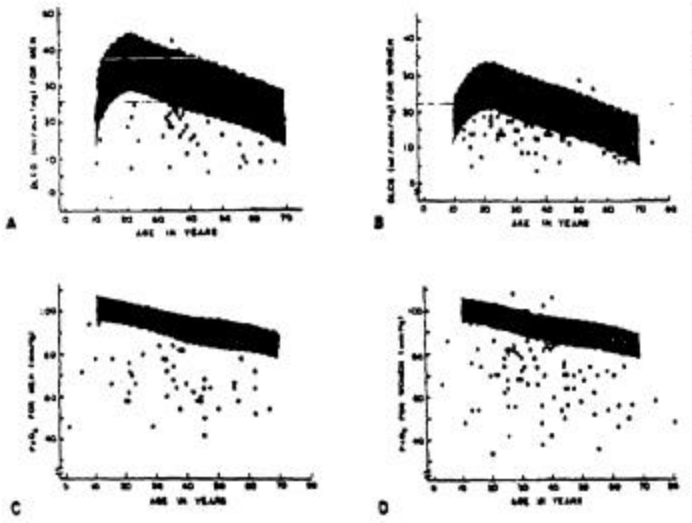


Figure 2. Distribution of findings for diffusing capacity of the lungs for carbon monoxide (D_LCO) in men (*A*) and women (*B*) is shown, with respect to the predicted values (± SD) (*shaded area*) based on age and the average American height for that age (7). Distribution of findings of arterial Po_2 with room air for men (*C*) and women (*D*) is shown, along with predicted values based on age and sex (10). Diffusing capacity was generally less than predicted, and hypoxemia was almost an ubiquitous finding.

changes of severe pulmonary hypertension. The commonest presenting symptoms, dyspnea and fatigue, were usually present more than 2 years before the diagnosis was made. However, because the sensation of dyspnea and fatigue occur commonly in active people, it is understandable that patients failed to seek medical attention early, or that physicians may have delayed in pursuing the diagnosis. We confirm a female-to-male predominance, although it is not as high as that found previously (15, 16). For the black patients in our registry, however, the female-to-male predominance was more pronounced, at 4.3:1. The registry also confirms that primary pulmonary hypertension may occur relatively late in life, with 9% of the patients having the diagnosis made at 60 or later (17). The incidence of familial cases was 6.4%. There were no distinctive features about these cases, with

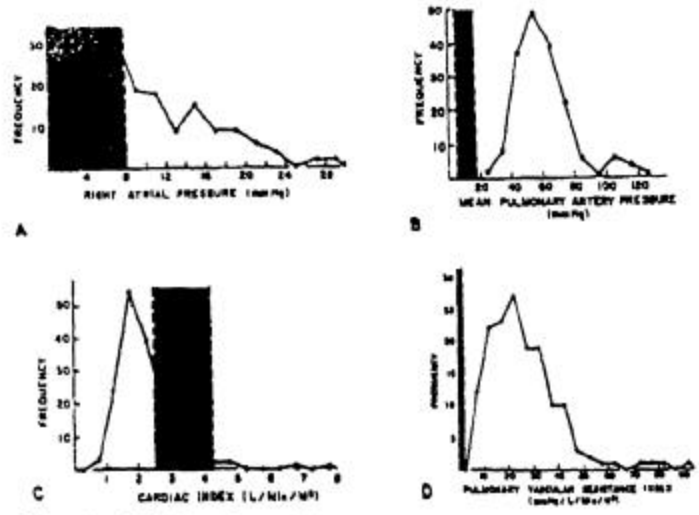


Figure 3. Distribution of hemodynamic findings is shown, in relation to published normal values (11). The right atrial pressure (*A*) was elevated in 72%. All patients, by definition, had an elevation in mean pulmonary artery pressure (*B*), with some having mean pulmonary artery pressures in excess of 100 mm Hg. The cardiac index (*C*) was reduced in 71% and reached a nadir value of 0.9 L/min · m². The pulmonary vascular resistance index (*D*) averaged 15 times greater than normal. Normal ranges are indicated by shaded regions.

the exception of shorter intervals from the onset of symptoms to diagnosis, which is probably a result of the patient's heightened awareness about the presenting symptoms of pulmonary hypertension.

Physical and noninvasive test findings correlated with the level of pulmonary hypertension in most patients. The presence of a right ventricular third sound was associated with a higher right atrial pressure and reduced cardiac output, and the presence of pulmonic insufficiency was associated with increased pulmonary artery pressures. The changes in the pulmonary vasculature noted in a chest radiograph correlated with all of these findings. Curiously, in approximately 6% of patients, the chest radiograph, echocardiogram, and electrocardiogram were relatively normal despite significant pulmonary hypertension, which underlines the lack of sensitivity of these tests in some patients.

Measurements of lung function showed that as a group, patients with primary pulmonary hypertension have a mild restrictive defect without obstruction, a reduced D_{LCO}, and hypoxemia with chronic respiratory alkalosis. Previous studies have described greater reductions in lung volume than in this series (17), but those patients would have been excluded before entry into the registry. The reduced D_{LCO} has been a common finding in these patients (18-20). Although obliteration of the small pulmonary arteries is one explanation for this reduction (21), no significant correlation was found in our patients between the D_{LCO} and any index of the severity of pulmonary hypertension. However, because of the wide distribution of measurements, with normal lung volumes and diffusing capacities a common finding, these tests are insensitive markers of the disease.

The almost universal finding of mild-to-moderate hypoxemia has been attributed to the effect of a low mixed venous P_{O_2} (resulting from the inadequate cardiac output), which amplified a mild degree of ventilation perfusion inequality (16). Severer degrees of hypoxemia have been attributed to right-to-left shunting through a patent foramen ovale. The chronic respiratory alkalosis we found has also been well described (18), and is usually attributed to increased afferent activity from intrapulmonary stretch receptors or intravascular baroreceptors (22, 23).

The data did not show a common cause for primary pulmonary hypertension. Neither pregnancy (24, 25) nor oral contraceptive use (26) appeared to be etiologic factors because their frequencies were similar to those of the general population. In addition, there were no apparent drug-related cases such as those that had occurred in Europe after the introduction of aminorex (11). There was a 29% incidence of a positive antinuclear antibody, but the frequency of Raynaud phenomenon, almost exclusively seen in the female patients, was only 11%, or slightly higher than the 6% reported in normal subjects (27). This incidence could, however, still be consistent with a type of primary pulmonary hypertension that presents as a collagen vascular disease affecting the lung (28). The female-to-male predominance of positive antinuclear antibodies is also consistent with findings from previous studies (28, 29).

There were two predominant patterns detected in perfusion lung scans in these patients. Although clinical-pathologic correlations have not yet been completed in the registry, previous studies that have described these patterns of perfusion lung scans in patients with unexplained pulmonary hypertension have suggested that the normal pattern represents plexiform lesions and that the patchy distribution indicates microthrombi or veno-occlusive disease (11, 30).

Analysis of the anatomic changes in the heart by M-mode echocardiography showed, as has been previously described, an increase in right ventricular size with characteristic changes in ventricular septal motion (31). Although it would be expected that the left ventricle would be uninvolved in primary pulmonary hypertension, the findings of the inverse relationship between left ventricular end-diastolic dimension and pulmonary vascular resistance index is interesting. Because the filling pressure of the left ventricle is, by definition, normal in primary pulmonary hypertension, this probably reflects the decreased volume loading of the left heart as determined by the severity of pulmonary vascular disease (32). Admittedly, the measurement of left ventricular size by M-mode echocardiography was not a highly sensitive measurement of pulmonary vascular resistance, although two-dimensional echocardiography may prove to be more accurate. If left ventricular size does reflect pulmonary vascular resistance, it may be useful to investigate the way in which this measurement might relate to the pathologic changes in the vascular bed or to patient survival.

The hemodynamic features of the patients entered showed severe elevations in pulmonary artery pressure and pulmonary vascular resistance. Right atrial pressure and cardiac index were abnormal in 72% and 71% of the patients, respectively, and were associated with clinical symptoms by New York Heart Association functional class. These same hemodynamic variables have been shown to reflect patient survival in primary pulmonary hypertension as well (33). The only difference between male and female patients was in resting heart rate, with the female patients averaging 7 beats/min faster than the male patients. However, previous studies done with normal populations have shown that female subjects normally have faster resting heart rates; thus, this factor cannot necessarily be attributed to the underlying disease (34).

The hemodynamic findings suggest that the severity of symptoms can be related to rising right atrial pressure and falling cardiac index, both of which are reflections of right ventricular function. The fact that the mean pulmonary artery pressure is of similar level in patients whose duration of symptoms is less than 1 year compared with those who were symptomatic for more than 3 years suggests that the pulmonary artery pressure rises to high levels during the course of disease. Patients whose only symptoms were dyspnea during exertion already had severe pulmonary hypertension with normal cardiac indexes. The onset of fatigue and edema, symptoms that reflect right ventricular failure, were more likely to appear later

in the clinical course. Although physicians tend to relate t severity of the disease with its duration of symptoms, this association was not evident when hemodynamic comparisons were made. Therefore, the severity of the disease process, as evidenced by histologic changes in the pulmonary vasculature, may not parallel the duration of symptoms of the disease, and the disease progression may differ considerably among patients.

An important function of the registry was to monitor the frequency of adverse consequences that might occur in the patients during their evaluation. No adverse consequences of lung perfusion scans were reported, and only one mild adverse consequence occurred in the 50 patients reported to have had pulmonary angiography. The fact that patients can have chronic proximal pulmonary thromboemboli mimicking primary pulmonary hypertension (35) underscores both the safety and necessity of ruling out chronic pulmonary thromboemboli in any patient who presents with unexplained pulmonary hypertension. Ten adverse consequences were reported to have been caused by catheterization used in diagnosis (excluding all drug evaluations), and six of the ten were probably related to the pulmonary hypertension itself. No deaths or sustained morbidity were associated with any of these procedures.

This registry has provided the characterization of the demographic and clinical features of a large number of patients with primary pulmonary hypertension. These data show that the disease is not usually diagnosed until advanced abnormalities are detected by physical examination, laboratory tests, or hemodynamic assessments of the pulmonary circulation. Although no curative therapy exists for primary pulmonary hypertension, we emphasize the need to focus on strategies of making an early diagnosis before these advanced abnormalities occur.

Appendix: Participating Clinical Centers

University of California, Cedars-Sinai Medical Center, Los Angeles, California (Spencer K. Koerner); University of California, San Diego, California (Kenneth M. Moser); University of California, San Francisco, California (Bruce H. Brundage, Thomas A. Ports); University of Colorado, Denver, Colorado (Berton M. Groves); Mount Sinai Medical Center, Miami Beach, Florida (Tahir Ahmed); University of Illinois, Chicago, Illinois (Stuart Rich); Johns Hopkins University, Baltimore, Maryland (Warren R. Summer); Harvard University, Children's Hospital, Boston, Massachusetts (Donald C. Fyler), Boston University, Boston, Massachusetts (Sharon Rounds); University of Michigan, Ann Arbor, Michigan (David R. Dietzker, John G. Weg); Henry Ford Hospital, Detroit, Michigan (Farzad Khaja); University of Minnesota, Minneapolis, Minnesota (Jay N. Cohn); St. Louis University, St. Louis, Missouri (Susan Marshall); Mayo Clinic, Rochester, Minnesota (Guy S. Reeder); University of Missouri, Kansas City, Missouri (Lee Rose); Creighton University, Omaha, Nebraska (Syed M. Muhiuddin). New York University Bellevue Medical Center, New York (Fredrick Feit); State University of New York, Stony Brook, New York (Adam Hurewitz); Columbia University, New York, New York (Robert B. Mellins, Robyn J. Barst); Cornell University Medical Center, New York, New York (Jeffrey Fisher); Mount Sinai Medical Center, New York, New York (Andreas Nicrchos, Valentin Fuster); Duke University, Durham, North Carolina (Robert H. Peter); University of Cincinnati, Cincinnati, Ohio (Noble O. Fowler); Oregon Health Sciences University, Portland, Oregon (Cecille Sunderland); Temple University, Philadelphia, Pennsylvania (Stanley B. Fiel); Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania (Alfred P. Fishman); Vanderbilt University, Nashville, Tennessee (John H. Newman); University of Texas, Houston, Texas (Gilbert D'Alonzo); Veterans Administration Hospital, Dallas, Texas (Lewis J. Rubin), LDS Hospital, Salt Lake City, Utah (C. Gregory Elliott); University of Washington, Seattle, Washington (David C. Ralph), Marshfield Clinic, Marshfield, Wisconsin (Michael J. Kryda).

Data and Coordinating Center: University of Illinois, Chicago, Illinois (Paul S. Levy, Sc.D., Stuart Rich, M.D.; Christopher Barker, Ph.D.; Geoffrey Page, Janet Kerns)

Pathology Center: University of Pennsylvania, Philadelphia, Pennsylvania (Guiseppe G. Pietra, M.D.)

National Heart, Lung, and Blood Institute: Carol E. Vreim, Ph.D.; Margaret Wu, Ph.D.

Steering Committee: Edward H. Bergofsky, M.D., Chairman; Stephen M. Ayres, M.D.; Bruce H. Brundage, M.D.; Katherine M. Detre, M.D., Dr P.H., Alfred P. Fishman, M.D.; Roberta M. Goldring, M.D., Berton M. Groves, M.D.; Paul S. Levy, Sc.D., Giuseppe G. Pietra, M.D., Lynne M. Reid, M.D.; Stuart Rich, M.D.; Carol E. Vreim, Ph.D.; George W. Williams, Ph.D.

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A COMPARISON OF CONTINUOUS INTRAVENOUS EPOPROSTENOL (PROSTACYCLIN) WITH CONVENTIONAL THERAPY FOR PRIMARY PULMONARY HYPERTENSION

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Abstract *Background.* Primary pulmonary hypertension is a progressive disease for which no treatment has been shown in a prospective, randomized trial to improve survival.

Methods. We conducted a 12-week prospective, randomized, multicenter open trial comparing the effects of the continuous intravenous infusion of epoprostenol (formerly called prostacyclin) plus conventional therapy with those of conventional therapy alone in 81 patients with severe primary pulmonary hypertension (New York Heart Association functional class III or IV).

Results. Exercise capacity was improved in the 41 patients treated with epoprostenol (median distance walked in six minutes, 362 m at 12 weeks vs. 315 m at base line), but it decreased in the 40 patients treated with conventional therapy alone (204 m at 12 weeks vs. 270 m at base line; $P<0.002$ for the comparison of the treatment groups). Indexes of the quality of life were improved only in the epoprostenol group ($P<0.01$).

Hemodynamics improved at 12 weeks in the epoprostenol-treated patients. The changes in mean pulmonary-artery pressure for the epoprostenol and control groups were −8 percent and +3 percent, respectively (difference in mean change, −6.7 mm Hg; 95 percent confidence interval, −10.7 to −2.6 mm Hg; $P<0.002$), and the mean changes in pulmonary vascular resistance for the epoprostenol and control groups were −21 percent and +9 percent, respectively (difference in mean change, −4.9 mm Hg per liter per minute; 95 percent confidence interval, −7.6 to −2.3 mm Hg per liter per minute; $P<0.001$). Eight patients died during the study, all of whom had been randomly assigned to conventional therapy ($P=0.003$). Serious complications included four episodes of catheter-related sepsis and one thrombotic event.

Conclusions. As compared with conventional therapy, the continuous intravenous infusion of epoprostenol produced symptomatic and hemodynamic improvement, as well as improved survival in patients with severe primary pulmonary hypertension. (N Engl J Med 1996;334:296-301.)

PRIMARY pulmonary hypertension is a disease characterized by the progressive elevation of pulmonary-artery pressure and vascular resistance, ultimately producing right ventricular failure and death.[1-3] A variety of treatments have been used, including vasodilators,[4-7] anticoagulant agents,[6,8] and lung or heart–lung transplantation,[9-13] but none have resulted in improved survival in a prospective, randomized trial.

Epoprostenol (formerly called prostacyclin or prostaglandin I_2) is a potent, short-acting vasodilator and inhibitor of platelet aggregation that is produced by vascular endothelium. Short-term infusions of epoprostenol decrease pulmonary vascular resistance in a dose-dependent manner in patients with primary pulmonary hypertension, and this response has been used to determine whether long-term oral vasodilator therapy is warranted.[14]

In an eight-week prospective, randomized trial, the continuous intravenous infusion of epoprostenol produced hemodynamic and symptomatic improvement.[15] Patients treated with epoprostenol for up to three years appeared to live longer than historical controls from the Registry on Primary Pulmonary Hypertension of the National Institutes of Health (NIH) who received standard therapy.[16] The objective of this study was to evaluate the effects of the continuous infusion of epoprostenol on exercise capacity, quality of life, hemodynamics, and survival in a 12-week open-label, prospective, randomized, multicenter study of patients with severe primary pulmonary hypertension who continued to be in New York Heart Association (NYHA) functional class III or IV despite conventional therapy.

METHODS

After giving their informed consent, 81 patients with primary pulmonary hypertension entered the study. We established a diagnosis in all patients before they entered, using the criteria of the Registry on Primary Pulmonary Hypertension of the NIH.[1] Patients were in NYHA functional class III or IV despite optimal medical therapy,

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*The members of the Primary Pulmonary Hypertension Study Group are listed in the Appendix.

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which consisted of the administration of anticoagulants, oral vasodilators, diuretic agents, cardiac glycosides, and supplemental oxygen. The primary objective was to evaluate the effects of the continuous infusion of epoprostenol on exercise capacity. Other major, prospectively defined objects of study were the effects of epoprostenol on survival and its effects on the quality of life. We also evaluated the effects of epoprostenol on hemodynamics.

Sterile, lyophilized epoprostenol sodium powder, synthesized by Upjohn (Kalamazoo, Mich.), was formulated by Wellcome Research Laboratories (Beckenham, Kent, United Kingdom) as flolan. Immediately before administration, epoprostenol was reconstituted with sterile glycine buffer (pH 10.5) and filtered.

Right-heart catheterization was performed in all patients with the use of standard techniques. After base-line hemodynamic variables were measured, epoprostenol was infused at an initial rate of 2 ng per kilogram of body weight per minute, with increments of 2 ng per kilogram per minute every 15 minutes. The infusion was discontinued at the dose that produced one or more of the following effects: a decrease of more than 40 percent in systemic arterial pressure, an increase of more than 40 percent in heart rate, or signs or symptoms deemed sufficient to warrant discontinuation of the infusion — that is, nausea, vomiting, severe headache, lightheadedness, or severe restlessness and anxiety. The infusion was subsequently reduced by 2 ng per kilogram per minute, and hemodynamic measurements were recorded at this maximal tolerated dose.

Randomization and Treatment

Eighty-one patients completed the short-term dose-ranging phase of the study and entered the 12-week study. One additional patient, in whom a pneumothorax developed during the base-line cardiac catheterization, was not enrolled in the study. A computer-generated, adaptive randomization was performed, with stratification according to the functional class, study center, and base-line vasodilator use.[17] Forty-one patients were randomly assigned to receive epoprostenol plus conventional therapy, and 40 patients were randomly assigned to receive conventional therapy alone. All the patients received oral anticoagulant agents during the study, with the exception of one patient in each treatment group. Adjustments in concomitant medications were allowed during the study on the basis of clinical judgment.

Venous access for the infusion of epoprostenol in the epoprostenol group was obtained by the insertion of a permanent catheter into a subclavian or jugular vein. Epoprostenol was infused continuously with the use of a portable infusion pump (CADD-1 Model 5100 HF, Pharmacia Deltec, St. Paul, Minn.). Before being discharged from the hospital, patients were trained in sterile technique, catheter care, and drug preparation and administration. Epoprostenol therapy was initiated at a dose of 4 ng per kilogram per minute below the maximal tolerated dose determined during dose ranging. Dose adjustments during the 12-week study were made on the basis of signs or symptoms consistent with clinical deterioration or the occurrence of adverse events. Hemodynamic measurements were repeated at the end of the study.

Exercise capacity was assessed at base line and at 1, 6, and 12 weeks with the use of the unencouraged six-minute-walk test.[18] The patients' quality of life was evaluated at base line and at 6 and 12 weeks with the Chronic Heart Failure Questionnaire, the Nottingham Health Profile, and the Dyspnea-Fatigue Rating.[19-21] Both the walk test and the quality-of-life instruments were administered by personnel not directly involved in patient care who were unaware of the treatment groups to which patients had been assigned. At the completion of the study, all patients were given the option of entering an open-label study of continuous epoprostenol therapy.

Statistical Analysis

Data are presented as means ±SE, medians, and 95 percent confidence intervals. Six-minute-walk data were analyzed in two intention-to-treat analyses: a nonparametric analysis of covariance and a parametric analysis of variance.[22] In the nonparametric analysis of covariance, patients who were unable to walk at base line were assigned a value of 0 m. Patients who had died or were unable to walk because of illness at week 12 were also assigned a value of 0 m. Patients who underwent transplantation during the study completed the exercise test at week 12, and the data on this test were included in the nonparametric analysis of covariance. An ordinary least-squares regression of the ranks of walking distance at week 12 was performed, with adjustment for covariates. The resulting residuals were analyzed with the use of the Cochran–Mantel–Haenszel procedure.

The parametric analysis of variance evaluated the changes from base line to week 12 in the distances walked. In this analysis, patients who died or received transplants before week 12 had their last observations (or six-minute-walk values before transplantation) carried forward and used as their values at week 12.

Survival was analyzed with the use of a log-rank test and included all the randomized patients. Survival analyses, adjusted for covariates, were based on the Cox regression model[23] and were performed both with data on some patients censored at transplantation and with such data not censored. For hemodynamic and quality-of-life measures, we determined the change from base line and constructed two-sided 95 percent confidence intervals[24,25] for the differences between treatment groups. In the Spearman analyses of the correlation between the changes from base-line six-minute-walk values and long-term hemodynamic effects, the last observation carried forward was used for patients who died or received transplants. A P value of less than 0.05 was considered to indicate statistical significance.

Results

The base-line demographic and hemodynamic characteristics of the two groups are shown in Table 1. There were no significant differences between the groups in the severity of pulmonary hypertension, duration of illness, use of concomitant medication, or NYHA functional class. The base-line distance in the six-minute walk was greater, though not significantly greater, in the epoprostenol group.

Effects of the Short-Term Infusion

The maximal short-term hemodynamic responses to infused epoprostenol are shown in Table 2. Only chang-

Table 1. Demographic and Hemodynamic Characteristics at Base Line, According to Treatment Group.*

Characteristic	Epoprostenol (N = 41)	Conventional Therapy (N = 40)
Age — yr	40±3	40±2
Sex — no. (%)		
Male	10 (24)	12 (30)
Female	31 (76)	28 (70)
NYHA functional class — no. (%)†		
III	31 (76)	29 (73)
IV	10 (24)	11 (28)
Months since diagnosis	32±8	25±6
Oral vasodilator therapy — no. (%)	27 (66)	24 (60)
Mean pulmonary-artery pressure — mm Hg	61±2	59±2
Mean right atrial pressure — mm Hg	13±1	12±1
Mean systemic-artery pressure — mm Hg	90±2	89±2
Mean pulmonary-capillary wedge pressure — mm Hg	10±1	10±1
Cardiac index — liter/min/m²	2.0±0.1	2.1±0.2
Heart rate — beats/min	79±2	86±2
Systemic arterial oxygen saturation — %	91±2	92±1
Mixed venous oxygen saturation — %	61±2	59±2
Stroke volume — ml/beat	46±3	45±4
Pulmonary vascular resistance — mm Hg/liter/min	16±1	16±1
Systemic vascular resistance — mm Hg/liter/min	25±1	24±1
6-min walk — m‡	316±18	272±23

*Plus–minus values are means ±SE. Percentages do not always sum to 100 because of rounding.

†NYHA denotes New York Heart Association.

‡The distance walked is meters in six minutes.

es in stroke volume and systemic vascular resistance were significantly different in the two treatment groups. The mean maximal tolerated dose of epoprostenol was 9.2±0.5 ng per kilogram per minute in the group subsequently assigned to receive epoprostenol and 7.6±0.5 ng per kilogram per minute in the conventional-therapy group. The initial dose in the patients treated with a long-term infusion of epoprostenol was 5.3±0.5 ng per kilogram per minute; the dose was increased to 9.2±0.8 ng per kilogram per minute by the end of the study.

Exercise Capacity

Exercise capacity was evaluated by measuring the change in the distance the patient could walk in six minutes from base line to week 12. The nonparametric analysis of covariance, with adjustment for the six-minute-walk values and the use of vasodilators at base line, showed that the median change from base line was an increase of 31 m in the epoprostenol-treated patients (median distance walked, 362 m at week 12 as compared with 315 m at base line) and a decrease of 29 m in the patients receiving conventional therapy (204 m at week 12 as compared with 270 m at base line; $P<0.002$ for the comparison of the treatment groups). Exercise capacity remained significantly improved ($P<0.02$) in the epoprostenol-treated patients after adjustment for both (1) the hemodynamic changes in stroke volume and systemic vascular resistance that resulted from the short-term infusion of epoprostenol (the only significant differences between the treatment groups) and (2) six-minute-walk values and vasodilator use at base line.

The mean distance walked increased by 32 m in the epoprostenol group (mean distance walked, 348±17 m at week 12 as compared with 316±18 m at base line) and decreased by 15 m in the conventional-therapy group (257±24 m at week 12 as compared with 272±23 m at base line; $P<0.003$ for the comparison of the treatment groups, as determined with a parametric analysis of variance).

There were significant inverse correlations between the change in the distance the patient could walk in six minutes and the corresponding changes in mean pulmonary-artery pressure, right atrial pressure, mean systemic-artery pressure, pulmonary vascular resistance, and systemic vascular resistance from base line to week 12. There were also significant correlations between the change in the six-minute-walk value and the corresponding changes in cardiac index and stroke volume from base line to week 12.

Table 2. Short-Term Hemodynamic Effects of Epoprostenol at the Maximal Tolerated Dose during Short-Term Dose Ranging.*

Variable	Change from Base Line		95% Confidence Interval†
	Epoprostenol (n = 41)	Conventional Therapy (n = 40)	
Mean pulmonary-artery pressure (mm Hg)	−2.4±1.1	−1.4±1.3	−4.4 to 2.4
Mean right atrial pressure (mm Hg)	−0.2±0.4	−1.3±0.6	−0.3 to 2.5
Mean systemic-artery pressure (mm Hg)	−13.6±1.5	−11.9±1.2	−5.5 to 2.2
Mean pulmonary-capillary wedge pressure (mm Hg)	1.5±0.9	1.0±0.8	−2.0 to 2.9
Cardiac index (liter/min/m²)	0.9±0.1	0.5±0.2	0.0 to 0.8
Heart rate (beats/min)	6.8±1.2	6.1±1.9	−3.7 to 5.1
Systemic arterial oxygen saturation (%)	−0.6±0.7	1.3±1.0	−4.2 to 0.5
Mixed venous oxygen saturation (%)	5.8±1.4	8.9±1.3	−7.0 to 0.9
Stroke volume (ml/beat)	14.8±2.7	5.8±3.0	1.1 to 17.0
Pulmonary vascular resistance (mm Hg/liter/min)	−5.5±0.8	−3.9±0.8	−4.0 to 0.7
Systemic vascular resistance (mm Hg/liter/min)	−10.3±0.9	−7.3±0.9	−5.7 to −0.6

*Plus–minus values are mean (±SE) changes from base line. The maximal tolerated doses were 9.2±0.5 ng per kilogram per minute in the epoprostenol group and 7.6±0.5 ng per kilogram per minute in the conventional-therapy group.

†95 percent confidence intervals are for the differences in mean changes between treatment groups. A confidence interval that does not contain zero indicates statistical significance.

Table 3. Effects on the Quality of Life of Treatment with Epoprostenol as Compared with Conventional Therapy.*

Treatment Effect	Change from Base Line					
	Epoprostenol		Conventional Therapy		Hodges–Lehmann Estimate†	95% Confidence Interval‡
	no. of patients	median change	no. of patients	median change		
Chronic Heart Failure Questionnaire§						
Dyspnea	35	8.0	26	0.0	7.0	4.0 to 10.0
Fatigue	39	5.0	31	0.0	5.0	3.0 to 7.0
Emotional function	38	6.0	30	−1.0	7.0	3.0 to 10.0
Mastery¶	39	3.0	30	−0.5	2.5	1.0 to 4.0
Nottingham Health Profile‖						
Emotional reaction	37	−10.0	31	0.0	−14.7	−24.5 to −4.9
Energy	39	−36.8	31	0.0	−36.8	−60.8 to 0.0
Pain	39	0.0	31	0.0	0.0	−5.8 to 0.0
Physical mobility	39	−11.2	30	−6.4	−9.2	−19.9 to 2.0
Sleep	41	−16.1	31	0.0	−21.7	−34.3 to −9.1
Social isolation	40	0.0	31	0.0	0.0	−20.1 to 0.0
Dyspnea-Fatigue Rating§	41	1.0	31	0.0	2.0	1.0 to 3.0

*Patients who died during the study were excluded from the quality-of-life analysis. For the three patients who underwent transplantation during the study, the 12-week quality-of-life assessment was performed after transplantation. For the two patients who discontinued the use of epoprostenol during the study, the 12-week quality-of-life assessment was performed at the end of the study.

†Hodges–Lehmann estimates[29] are estimates of the true median changes from base line.

‡95 percent confidence intervals are for comparisons between treatment groups. A confidence interval that does not contain zero indicates statistical significance.

§Positive values for changes indicate improvements over base-line values.

¶Mastery is defined as a patient's feeling of control over his or her disease.

‖Negative values for changes indicate improvements over base-line values.

Clinical and Hemodynamic Measures

The results of assessments of quality of life are shown in Table 3. Patients who received epoprostenol for 12 weeks had significant improvements in all four parts of the Chronic Heart Failure Questionnaire, in two of the six parts of the Nottingham Health Profile, and in the Dyspnea-Fatigue Rating ($P<0.01$).

Functional class was assessed in all patients who were alive and had not received transplants by the end of the 12-week study period (40 in the epoprostenol group and 31 in the conventional-therapy group). In the epoprostenol group, the functional class improved

in 16 patients (40 percent), worsened in 5 (13 percent), and was unchanged in 19 (48 percent). In the conventional-therapy group, in contrast, the functional class improved in only 1 patient (3 percent), worsened in 3 (10 percent), and was unchanged in 27 (87 percent; $P<0.02$ for the comparison of the treatment groups).

The changes in the hemodynamic measures from base line to week 12 are shown in Table 4. Comparisons of the treatments showed that the epoprostenol-treated patients had significant improvement in mean pulmonary-artery pressure, cardiac index, and pulmonary vascular resistance. The changes in mean pulmonary-artery pressure for the epoprostenol and control groups were −8 percent and +3 percent, respectively ($P<0.002$), and the mean changes in pulmonary vascular resistance were −21 percent and +9 percent, respectively ($P<0.001$).

Transplantation and Survival

Three patients underwent lung transplantation during the 12-week study: one epoprostenol-treated patient at 11 days and two patients treated with conventional therapy at 63 and 68 days. All three were alive at the end of the study. Therapy for two patients randomly assigned to receive epoprostenol was discontinued before the end of the study: in one patient, because of adverse effects (jaw pain and diarrhea), and in the other, because the patient was unable to manage the drug-delivery system.

Eight patients died during the 12-week study; all were in the conventional-therapy group ($P=0.003$) (Fig. 1). Among those who died, there was an equal distribution of patients in NYHA functional classes III and IV. The six-minute-walk values at base line were significantly lower in these 8 patients than in the 73 survivors in both groups (195±63 m vs. 305±14 m, $P<0.03$). There were, however, no significant differences in base-line hemodynamic variables or short-term responses during dose ranging between the survivors in both treatment groups and the eight patients who died. Performance in the six-minute walk at base line was an independent predictor of survival ($P<0.05$); however, survival remained significantly improved in the epoprostenol group after adjustment for that variable ($P<0.002$). Survival also remained significantly improved in the epoprostenol group ($P<0.001$) after adjustment for the changes in stroke volume and in systemic vascular resistance in response to the short-term infusion of epoprostenol (the only significant differences between treatment groups).

Complications

Minor complications related to the use of epoprostenol were frequent and included jaw pain, diarrhea, flushing, headaches, nausea, and vomiting. Serious complications were most often due to the delivery system and included four episodes of nonfatal, catheter-related sepsis and one nonfatal thrombotic event (a paradoxical embolism). There were 26 episodes of malfunction of the drug-delivery system resulting in temporary interruption of the infusion. These included occlusions, perforations, and dislodgements of the catheter and pump malfunction. While epoprostenol therapy was interrupted, patients experienced an increase in their symptoms. Additional problems related to the delivery system included irritation or infection at the catheter site in seven patients, bleeding at the catheter site in four, and catheter-site pain in four.

Discussion

Since the description of the characteristic hemodynamic abnormalities over 40 years ago, primary pulmonary hypertension has been regarded as a progressive disease that is usually refractory to treatment.[25] In the present study, a randomized, controlled trial, we documented improvement in exercise capacity and survival in patients with severe primary pulmonary hypertension who were treated with epoprostenol in addition to conventional therapy, as compared with patients treated with conventional therapy alone. The eight patients who died had been randomly assigned to the conventional-therapy group, and all died as a result of their underlying pulmonary vascular disease. Even when these patients were excluded from the analyses of exercise-test results, exercise capacity remained significantly improved in the epoprostenol-treated patients as compared with the conventional-therapy group. In addition, hemodynamic function and exercise capacity tended to deteriorate or remain unchanged with conventional ther-

Table 4. Hemodynamic Effects of Epoprostenol or Conventional Therapy at 12 Weeks.*

Variable	Change from Base Line		Difference between Treatments	95% Confidence Interval†
	Epoprostenol	Conventional therapy		
Mean pulmonary-artery pressure (mm Hg)	−4.8±1.3	1.9±1.6	−6.7	−10.7 to −2.6
Mean right atrial pressure (mm Hg)	−2.2±1.1	0.1±0.9	−2.3	−5.2 to 0.7
Mean systemic-artery pressure (mm Hg)	−4.8±2.1	−0.9±1.7	−3.9	−9.6 to 1.7
Mean pulmonary-capillary wedge pressure (mm Hg)	0.4±1.2	−1.0±1.6	1.4	−2.5 to 5.3
Cardiac index (liter/min/m²)	0.3±0.1	−0.2±0.2	0.5	0.2 to 0.9
Heart rate (beats/min)	−0.9±2.5	−1.8±1.5	0.9	−5.2 to 7.2
Systemic arterial oxygen saturation (%)	2.0±1.6	−0.6±1.4	2.6	−1.8 to 7.1
Mixed venous oxygen saturation (%)	1.2±1.8	−2.6±2.0	3.8	−1.6 to 9.2
Stroke volume (ml/beat)	6.6±2.2	−3.5±3.3	10.1	2.5 to 17.8
Pulmonary vascular resistance (mm Hg/liter/min)	−3.4±0.7	1.5±1.2	−4.9	−7.6 to −2.3
Systemic vascular resistance (mm Hg/liter/min)	−4.0±1.0	2.1±1.4	−6.1	−9.5 to −2.8

*The minus values are the mean (±SE) changes from base line. Patients who died or underwent transplantation during the study, as well as the two patients who discontinued epoprostenol during the study, were excluded from the hemodynamic analysis.

†95 percent confidence intervals are for comparisons between treatment groups. A confidence interval that does not contain zero indicates statistical significance.

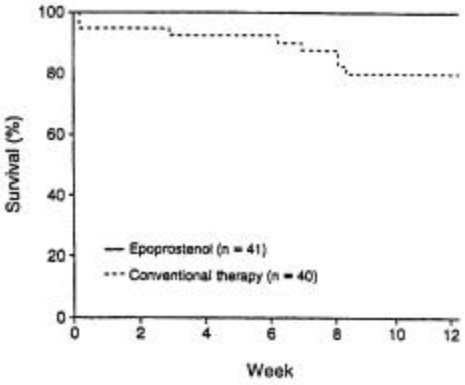

Figure 1. Survival among the 41 Patients Treated with Epoprostenol and the 40 Patients Receiving Conventional Therapy.
Data on patients who underwent transplantation during the 12-week study were censored at the time of transplantation. Estimates were made by the Kaplan–Meier product-limit method. The two-sided *P* value from the log-rank test was 0.003. Survival analysis with data on patients receiving transplants not censored at transplantation resulted in the same level of significance (two-sided $P = 0.003$ by the log-rank test).

apy, whereas it was consistently improved with the use of epoprostenol.

The rationale for using continuous epoprostenol infusion to treat primary pulmonary hypertension was based initially on the demonstration that epoprostenol is a potent pulmonary vasodilator when administered to laboratory animals with acute pulmonary vasoconstriction induced by constrictor stimuli.[27,28] Our results, consistent with these findings, indicate that the short-term infusion of epoprostenol reduces pulmonary-artery pressure and pulmonary vascular resistance in patients with primary pulmonary hypertension. However, randomization in this and in our previous study[15] was performed independently of the short-term responses to epoprostenol during dose ranging, and we have previously observed that long-term effects are frequently seen even in the patients in whom no short-term changes were manifested.[15,16] Thus, the long-term effects of epoprostenol in primary pulmonary hypertension may be only partially related to its vasodilator properties and may be due, at least in part, to poorly defined effects on vascular growth, remodeling, or platelet function.[29-32] Unlike the use of other vasodilators to treat pulmonary hypertension (which should be reserved for patients who have short-term pulmonary vasoreactivity),[4,5,7] the use of continuous intravenous epoprostenol may be worth investigating in patients who continue to have severe symptoms despite conventional therapy, even if they have no short-term response to epoprostenol or if their condition has deteriorated with conventional therapy.

Several factors have been shown to determine survival in patients with primary pulmonary hypertension, including hemodynamic variables and functional class.[2,3] Determining the status of these factors may be helpful when one is selecting and timing a more aggressive approach to treatment, such as transplantation. In this study, we found that performance in the six-minute walk at base line was also an independent predictor of survival. Thus, assessing exercise capacity in this inexpensive and noninvasive way may be useful in determining whether alternative treatment options should be considered in individual patients.

Since epoprostenol is unstable at pH values below 10.5, it cannot be given orally, and continuous intravenous infusion is necessary because of its short half-life in the circulation.[33] Although the delivery system for continuous infusion is complex, most patients were capable of learning how to prepare and infuse the drug. Only one patient was withdrawn from this study because of the inability to master drug delivery. Despite the cumbersome nature of treatment with epoprostenol, the patients' quality of life was significantly improved. Thus, the complexity of the treatment may be offset by the overall improvement in well-being in most patients.

Continuous intravenous epoprostenol therapy is not, however, devoid of potentially serious complications (most of which are attributable to the delivery system), including catheter-related infections, thrombosis, and temporary interruption of the infusion due to malfunction of the pump. Although these adverse events were not associated with death in this study, they are potentially life-threatening and underscore the need for an alternative mode of drug delivery.

The principal limitation of this study was that it was not a double-blind, placebo-controlled trial. Therefore, we cannot completely exclude the possibility of investigator or patient bias, particularly with regard to exercise capacity. We felt we could not design this study as a double-blind, placebo-controlled trial because of ethical considerations based on the known incidence of sepsis caused by central venous catheters in control patients[34,35] and because unique or highly predictable symptoms during long-term epoprostenol treatment — that is, jaw pain and diarrhea — prevented the blinding of physicians and patients.

The changes in stroke volume and systemic vascular resistance during the short-term infusion of epoprostenol were greater in the group subsequently assigned to receive the drug, raising the possibility that these patients had greater vasoreactivity at base line. However, none of the hemodynamic variables that are predictors of survival (pulmonary-artery pressure, right atrial pressure, cardiac index, and mixed venous oxygen saturation)[2,8] and none of the markers of pulmonary vasoreactivity with short-term vasodilator testing (short-term changes in pulmonary-artery pressure, cardiac index, and pulmonary vascular resistance)[4,5,7] were different in the two groups.

An additional limitation of this study is the suggestion that the base-line exercise capacity of the patients randomly assigned to receive conventional therapy was slightly worse than that of the patients assigned to re-

ceive epoprostenol. Although these differences were not statistically significant, it is possible that the epoprostenol-treated patients may have been less impaired at base line. On the basis of our observation that exercise capacity is an independent predictor of survival in patients with primary pulmonary hypertension, future trials should include randomization based on performance in the six-minute walk at base line in addition to other known predictors of survival.

In conclusion, the continuous intravenous infusion of epoprostenol plus conventional therapy for primary pulmonary hypertension resulted in better hemodynamics, exercise endurance, quality of life, and survival than conventional therapy alone. Although we did not address the long-term effects of therapy, our previous study suggests that the beneficial effects of epoprostenol on hemodynamics and exercise capacity persist with long-term therapy.[16] When epoprostenol is used as a bridge to transplantation, stabilizing the patient's hemodynamics could lower perioperative rates of morbidity and mortality. The continuous intravenous infusion of epoprostenol may be useful in the management of severe primary pulmonary hypertension when it is refractory to conventional medical therapy.

We are indebted to the study coordinators and pharmacists who participated in this trial for their technical assistance.

Appendix

Other participants in the North American Primary Pulmonary Hypertension Study included E. Horn and J. Kirkpatrick, Columbia–Presbyterian Medical Center, New York; K. Wynne, University of Colorado Health Sciences Center, Denver; W. Knight, University of Alabama Medical Center, Birmingham; D. Georgiou and J. Beckman, Harbor–UCLA Medical Center, Torrance, Calif.; W.R. Clarke, D. Ralph, and P. Schrader, Children's Hospital and University Hospital, University of Washington, Seattle; E.J. Caldwell, W. Williams, and B. Vogel, Maine Medical Center, Portland; N.A. Ettinger and D. Canfield, Barnes Hospital, Washington University, St. Louis; N.S. Hill and C. Carlisle, Rhode Island Hospital, Providence; A. Hinderliter and P.W. Willis IV, University of North Carolina Hospitals, Chapel Hill; A.E. Frost and K. Chafizedah, Methodist Hospital, Baylor College of Medicine, Houston; D. Ross and D. Claire, Cedars–Sinai Medical Center, Los Angeles; E. Shalit, Sir Mortimer B. Davis Jewish General Hospital, McGill University, Montreal; B. Edwards, C. Severson, and K. Kosberg, Mayo Medical Center, Rochester, Minn.; T. Tokarczyk, Presbyterian–University Hospital, University of Pittsburgh, Pittsburgh; L. Kaufman, University of Illinois at Chicago; L. Hartle, University of Maryland School of Medicine, Baltimore; W.R. Summer, B. deBoisblanc, and B. Everett, Charity Hospital, Louisiana State University Medical Center, New Orleans; and A. Krichman, Duke University Medical Center, Durham, N.C.

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Continuous Intravenous Epoprostenol for Pulmonary Hypertension Due to the Scleroderma Spectrum of Disease

A Randomized, Controlled Trial

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Background: Pulmonary hypertension is a progressive and often fatal complication of the scleroderma spectrum of disease for which no treatment has been proven effective in a randomized trial.

Objective: To determine the effect of epoprostenol on pulmonary hypertension secondary to the scleroderma spectrum of disease.

Design: Randomized, open-label, controlled trial.

Setting: 17 pulmonary hypertension referral centers.

Patients: 111 patients with moderate to severe pulmonary hypertension.

Intervention: Epoprostenol plus conventional therapy or conventional therapy alone.

Measurements: The primary outcome measure was exercise capacity. Other measures were cardiopulmonary hemodynamics, signs and symptoms of pulmonary hypertension and scleroderma, and survival.

Results: Exercise capacity improved with epoprostenol (median distance walked in 6 minutes, 316 m at 12 weeks compared with 270 m at baseline) but decreased with conventional therapy (192 m at 12 weeks compared with 240 m at baseline). The difference between treatment groups in the median distance walked at week 12 was 108 m (95% CI, 55.2 m to 180.0 m) ($P < 0.001$). Hemodynamics improved at 12 weeks with epoprostenol. The changes in mean pulmonary artery pressure for the epoprostenol and conventional therapy groups were −5.0 and 0.9 mm Hg, respectively (difference, −6.0 mm Hg [CI, −9.0 to −3.0 mm Hg), and the mean changes in pulmonary vascular resistance were −4.6 and 0.9 mm Hg/L per minute, respectively (difference, −5.5 mm Hg/L per minute [CI, −7.3 to −3.7 mm Hg/L per minute). Twenty-one patients treated with epoprostenol and no patients receiving conventional therapy showed improved New York Heart Association functional class. Borg Dyspnea Scores and Dyspnea-Fatigue Ratings improved in the epoprostenol group. Trends toward greater improvement in severity of the Raynaud phenomenon and fewer new digital ulcers were seen in the epoprostenol group. Four patients in the epoprostenol group and five in the conventional therapy group died (*P* value not significant). Side effects of epoprostenol therapy included jaw pain, nausea, and anorexia. Adverse events related to the epoprostenol delivery system included sepsis, cellulitis, hemorrhage, and pneumothorax (4% incidence for each condition).

Conclusions: Continuous epoprostenol therapy improves exercise capacity and cardiopulmonary hemodynamics in patients with pulmonary hypertension due to the scleroderma spectrum of disease.

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Pulmonary hypertension is characterized by progressive elevation of pulmonary artery pressure and vascular resistance, often leading to right ventricular failure and death (1–3). Continuous intravenous infusion of epoprostenol improves prognosis and symptoms in patients with primary (idiopathic) pulmonary hypertension (4–8). Randomized, con-

See related article on pp 435-443 and editorial comment on pp 500-502.

Table 1. Key Inclusion and Exclusion Criteria

Inclusion criteria
Diagnosis of the scleroderma spectrum of disease
Age ≥ 16 y
Able to walk at least 50 m in 6 minutes at baseline
Moderate to severe pulmonary hypertension with the following conditions
Mean pulmonary arterial pressure ≥ 35 mm Hg
Pulmonary vascular resistance ≥ 3 mm Hg/L per minute
Right atrial pressure ≤ 20 mm Hg
Absence of congenital heart disease
Pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤ 15 mm Hg. If it was not possible to measure the pulmonary capillary wedge pressure or left ventricular end-diastolic pressure, echocardiographic criteria to exclude left heart disease were applied.
Ventilation–perfusion lung scan or pulmonary angiography not indicative of thromboembolic disease
Pulmonary function tests or high-resolution computed tomography scanning showing no more than mild interstitial lung disease
Exclusion criteria
Any new long-term therapy for pulmonary hypertension or the scleroderma spectrum of disease added within the past month
Any medication used to treat pulmonary hypertension or the scleroderma spectrum of disease discontinued within the last week, except anticoagulant agents
Any type of current prostaglandin therapy

trolled clinical trials of epoprostenol for secondary pulmonary hypertension have not been conducted.

Pulmonary hypertension frequently complicates the scleroderma spectrum of disease, which includes diffuse scleroderma, limited scleroderma (the CREST syndrome [calcinosis cutis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangectasia]), and the overlap syndrome. These multisystem diseases are characterized by connective tissue and vascular abnormalities; vascular lesions are prominent in all affected tissues (9). Pulmonary hypertension occurs in up to 33% of patients with diffuse scleroderma and 10% to 50% of those with the CREST syndrome (10, 11), in which it is one of the leading causes of death (12, 13). Pulmonary hypertension in the scleroderma spectrum of disease may be associated with interstitial pulmonary fibrosis or may consist of a direct involvement of small and medium-sized pulmonary arteries and arterioles with smooth-muscle hyperplasia, medial hypertrophy, and intimal proliferation (10, 13, 14). Principal involvement of the pulmonary vasculature is more common in the CREST syndrome, whereas patients with pulmonary hypertension and diffuse scleroderma more often have interstitial lung disease (13).

No therapies have been proven effective for pulmonary hypertension secondary to the scleroderma spectrum of disease. Small numbers of patients have responded to captopril (15), nifedipine (16–20), and prazosin. In a short-term study of intravenous epoprostenol in seven patients with scleroderma (two with diffuse scleroderma and five with limited scleroderma), six had a decrease in mean pulmonary artery pressure and pulmonary vascular resistance (21). In a small study of pulmonary hypertension secondary to connective tissue disease, long-term infusion therapy with a prostacyclin analogue, iloprost, resulted in improvement in New York Heart Association (NYHA) functional class and quality of life but a variable hemodynamic response (22). Results from a single-center, uncontrolled study suggest that long-term, continuously infused epoprostenol therapy can produce hemodynamic and symptomatic responses in patients with connective tissue disease who have severe pulmonary hypertension that is refractory to conventional medical therapy (23).

The rationale for using continuous epoprostenol infusion to treat pulmonary hypertension secondary to the scleroderma spectrum of disease was based on the efficacy of this therapy for primary pulmonary hypertension (4–8) and recognition that scleroderma is a disease characterized by vasospasm and structural changes in the walls of blood vessels. Prostacyclin is a naturally occurring substance produced by vascular endothelium that has vasodilating, antiplatelet aggregation, and cytoprotective effects (24–33). Endogenous production of prostacyclin is decreased in an animal model of neonatal pulmonary hypertension (34) and in adult humans with pulmonary hypertension (35). Continuous infusion of prostacyclin normalizes plasma markers of endothelial cell injury and platelet aggregation in patients with primary pulmonary hypertension (36). Endothelial dysfunction also plays an important role in the vascular manifestations of the scleroderma spectrum of disease (37, 38), including the Raynaud phenomenon and digital ischemia, which cause considerable morbidity. Calcium-channel blockers (39–45), enalapril (46), and intermittent intravenous infusions of prostacyclin (47–49) and iloprost (50–54) improve the Raynaud phenomenon in some patients. Mixed results have been obtained with oral prostacyclin analogues (55, 56), and a recent multicenter trial of oral iloprost showed no benefit (57). The effect of long-term, continuously infused epoprostenol on the severity of the Raynaud phenomenon and on digital ulcer counts has not been previously evaluated.

Our 12-week multicenter, open-label, randomized study was designed to determine whether the beneficial effect of epoprostenol seen in patients with primary pulmonary hypertension could be extended to patients with pulmonary hypertension secondary to the scleroderma spectrum of disease. Our objective was to evaluate the effects of continuous infusion of epoprostenol on exercise capacity in patients with pulmonary hypertension secondary to the scleroderma spectrum of disease. A secondary objective was assessment of the effects of long-term continuous epoprostenol infusion on cardiopulmonary hemodynamics, Borg Dyspnea Score, Dyspnea-

Fatigue Rating, NYHA functional class, survival, and safety. Vasospastic manifestations, such as the Raynaud phenomenon and digital ulcerations, were also followed.

Methods

Patient Selection

Eligible patients had pulmonary hypertension secondary to the scleroderma spectrum of disease in accordance with the inclusion and exclusion criteria summarized in **Table 1**. For the purposes of this study, the scleroderma spectrum of disease was defined as systemic sclerosis with diffuse or limited scleroderma (58); systemic sclerosis that overlapped with another connective tissue disease; or the presence of definite features of systemic sclerosis, including the Raynaud phenomenon and positive test result for antinuclear antibody, plus positive test results for anticentromere antibody, anti–Scl 70 antibody, or nailfold capillary abnormalities. Systemic sclerosis with limited cutaneous involvement (the CREST syndrome) was defined as the presence of any three of the following conditions: subcutaneous calcinosis, the Raynaud phenomenon, esophageal dysfunction (defined clinically), sclerodactyly, or telangectasia. Patients with interstitial lung disease of a more than mild degree were not included in the study because such patients were thought to be less likely to show benefit.

On the basis of a previous 12-week study of the effects of epoprostenol infusion in patients with severe primary pulmonary hypertension (6) and using the 6-minute walk test as the primary outcome measure, we calculated that 50 patients per treatment group would provide 80% power to detect a difference of 50 meters in the average change from baseline, at an α level of 0.05 (two-tailed t-test).

Randomization and Treatment

The protocol was approved by the institutional review boards of the 17 participating centers. After giving informed consent, 111 eligible patients were randomly assigned (1:1) to receive continuous epoprostenol infusion (Flolan, Glaxo Wellcome, Inc., Research Triangle Park, North Carolina) plus conventional therapy or to receive conventional therapy alone. Investigators contacted a central randomization center to obtain treatment assignment, which was based on a stratified randomized block design. Assignments were stratified on the basis of vasodilator use at baseline (yes or no) and exercise capacity at baseline (50 to <200 m or ≥200 m) and were randomized within blocks. Fifty-six patients were assigned to receive epoprostenol plus conventional therapy, and 55 patients were assigned to receive conventional therapy alone. Investigators were not blinded to treatment group assignment; however, independent blinded observers assessed the primary efficacy measure, exercise capacity. Patients taking calcium-channel blockers at study entry continued to take them during the study period. Adjustment in concomitant medications were allowed during the study on the basis of clinical judgment. Patients in both groups were to receive oral anticoagulants during the study; 94 of the 111 enrolled patients took warfarin.

Venous access for epoprostenol infusion (in the epoprostenol group only) was obtained by insertion of a permanent indwelling central venous catheter. Epoprostenol was infused continuously by a portable infusion pump (CADD-1 Model 5100 HF, SIMS Deltec, St. Paul, Minnesota). Patients were instructed in sterile technique, catheter care, and drug preparation and administration. Epoprostenol therapy was initiated at a low dose (usually ≤2 ng/kg of body weight per minute). During the 12-week study, doses were adjusted on the basis of signs or symptoms consistent with persistent pulmonary hypertension in the absence of intolerable adverse effects (**Figure 1**).

Outcome Measures

The primary measure of efficacy was exercise capacity, as defined by the distance a patient could walk in 6 minutes. Trained observers at each site who were not otherwise involved in patient care administered the 6-minute walk test. All patients wore an ambulatory infusion pump and a hospital gown over their clothes to mask the presence or absence of a long-term indwelling catheter, thereby blinding testers to the patients' treatment groups. Each patient performed one practice walk test. A standardized, unencouraged 6-minute walk test was performed as described elsewhere (59) at baseline and at 1, 6, and 12 weeks. The 6-minute walk test

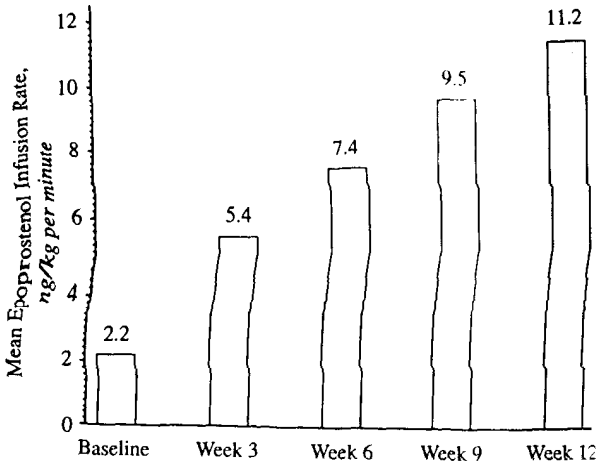

Figure 1. Epoprostenol dosing. Numbers at the tops of the bars represent exact mean rates.

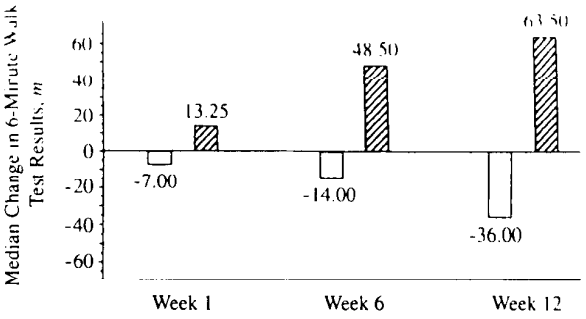

Figure 2. Median change from baseline in results of the 6-minute walk test at weeks 1, 6, and 12. Nonparametric analysis of covariance with adjustment for 6-minute walk values and use of vasodilators at baseline showed that the median distance walked in 6 minutes increased in patients who received epoprostenol (*striped bars*) compared with patients who received conventional therapy (*white bars*) at weeks 6 ($P = 0.003$) and 12 ($P < 0.001$).

has been shown to provide meaningful outcome data in assessing potential therapy for patients with pulmonary hypertension (6).

Secondary measures of efficacy were cardiopulmonary hemodynamics measured by performing right-heart catheterization using standard techniques at baseline and week 12; the Borg Dyspnea Score (60), obtained immediately after completion of the 6-minute walk test at baseline and 1, 6, and 12 weeks (6, 59); the Dyspnea-Fatigue Rating, obtained before the 6-minute walk test at baseline and weeks 1, 6, and 12 (61); NYHA functional class (62), measured at baseline and weeks 1, 6, and 12; digital ulcer counts, done at baseline and weeks 6 and 12; and the severity of the Raynaud phenomenon, assessed weekly. For determination of the Raynaud phenomenon severity score, patients were asked to score the severity of their Raynaud disease, taking into account the number of attacks per day, the duration of attacks, symptoms (such as numbness, burning, pain, and tingling), hand disability caused by the attack (but not by pain, ulcers, arthritis, or scleroderma skin), and influence of cold and stress exposure on daily activity and sense of well-being. Patients were asked to circle the number from 1 (no problems) to 10 (severe problems) that best described the severity of their Raynaud phenomenon over the past week. Only new digital ulcers were counted. Survival was also determined.

Safety was assessed by comparison of adverse experiences in the two treatment groups and by laboratory assessments (including hemoglobin level; platelet count; leukocyte count; serum creatinine concentration; and levels of blood urea nitrogen, alkaline phosphatase, and alanine aminotransferase) at baseline and week 12. An independent Data Safety and Monitoring Board reviewed safety data (including adverse effects and fatal events) after 15, 35, and 70 patients had completed the study.

Statistical Analysis

Categorical data are presented as frequencies and percentages by treatment group. Continuous data are presented as the mean ± SE or the median. Six-minute walk data were analyzed in two intention-to-treat analyses: a nonparametric analysis of covariance (63), which was the primary analysis, and a parametric analysis of variance. In the nonparametric analysis of covariance, patients who had died or were unable to walk because of illness were assigned a value of 0 meters. An ordinary least-squares regression of the ranks of the distance walked at baseline compared with week 12 was performed, adjusting for baseline walk category (< 200 m or ≥200 m) and vasodilator use (yes or no). The resulting residuals from the regression were analyzed by using the Cochran–Mantel–Haenszel test statistic, controlling for baseline walk category and vasodilator use. The parametric analysis of variance evaluated the change from baseline to week 12 in the distance walked. Patients at week 12 who had died or were too ill to walk had their last observations carried forward and used as their value at week 12.

Hemodynamic variables were analyzed by calculating the change from baseline to week 12 for each patient. The difference in mean change between treatment groups was calculated, and a 95% parametric CI was derived by using a Student *t*-distribution. The Dyspnea-Fatigue Rating and the Borg Dyspnea Score were analyzed by calculating the change from baseline to week 12 for each patient. The difference in median change (Hodges–Lehmann estimate) between treatment groups was calculated and a two-sided 95% CI was derived by using a nonparametric Wilcoxon rank-sum statistic (64). New York Heart Association functional class was analyzed by categorizing a shift from baseline to week 12 (for example, class IV at baseline to class II at week 12).

The Raynaud phenomenon was analyzed by first ranking the severity scores across all patients without regard to treatment at each time point. Each patient's average rank across time points was then calculated. The average ranks were compared by using a Cochran–Mantel–Haenszel test statistic. This method was an area under the curve analysis on a rank scale. Only patients who had at least one attack of Raynaud disease during the study were included. Patients who did not have an attack during a specific time period were assigned a value of 0. Digital ulcers were summarized by the number of patients with one or more new ulcers over the 12-week period and by the total number of new ulcers over the 12-week period.

Survival analyses were based on the Kaplan–

Table 2. Demographic and Hemodynamic Characteristics at Baseline*

Characteristic	Epoprostenol Group	Conventional Therapy Group
Age, *y*	53.0 ± 13.1	57.3 ± 10.3
Sex, *n (%)*		
Male	5 (9)	10 (18)
Female	51 (91)	45 (82)
NYHA functional class, *n (%)*		
II	1 (2)	4 (7)
III	42 (75)	45 (82)
IV	13 (23)	6 (11)
Time since pulmonary hypertension diagnosis, *mo*	14.5 ± 17.9	15.2 ± 20.1
Classification of scleroderma spectrum of disease, *n (%)*		
Diffuse scleroderma	7 (13)	7 (13)
Limited scleroderma	38 (68)	39 (71)
Overlap syndrome	8 (14)	6 (11)
Features of scleroderma	3 (5)	3 (5)
Time since diagnosis of scleroderma spectrum of disease, *mo*	85.9 ± 93.0	94.8 ± 102.8
Oral vasodilator therapy, *n (%)*	38 (68)	38 (69)
Current use of anorexigens, *n (%)*	0 (0)	0 (0)
Past exposure to anorexigens, *n (%)*	8 (14)	6 (11)
Mean pulmonary arterial pressure, *mm Hg*	50.9 ± 10.6	49.1 ± 10.2
Mean right atrial pressure, *mm Hg*	13.1 ± 5.0	11.1 ± 5.5
Mean systemic arterial pressure, *mm Hg*	92.8 ± 12.4	89.1 ± 10.8
Cardiac index, *L/min per m²*	1.9 ± 0.6	2.2 ± 0.7
Heart rate, *beats/min*	83.7 ± 10.9	84.5 ± 13.5
Systemic arterial oxygen saturation, %	92.7 ± 6.8	92.5 ± 6.6
Mixed venous oxygen saturation, %	57.4 ± 10.8	58.8 ± 9.9
Pulmonary vascular resistance, *mm Hg/L per minute*	14.2 ± 7.1	11.2 ± 5.3
Median distance walked in 6 minutes, *m*	271.5	240.0

* Values with a plus/minus symbol are the mean ± SD. NYHA = New York Heart Association.

Meier method (65) and were performed both with patient data censored at time of withdrawal (death or discontinuation) and with the same data not censored. The log-rank test was used to assess treatment differences.

Role of the Funding Source

The funding source for the study, Glaxo Wellcome, Inc., assisted in the collection, gathering, and analysis of data and was aware of the decision to submit the paper for publication.

Results

Comparability of Study Groups at Baseline

Baseline demographic and hemodynamic characteristics of the two groups are shown in **Table 2**. The groups did not differ significantly in severity of pulmonary hypertension, duration of illness, or NYHA functional class. Six patients (11%) in the conventional therapy group and 8 (14%) in the epoprostenol group had been previously exposed to anorectic agents. Sixteen patients (29%) in the conventional therapy group and 10 (18%) in the epoprostenol group were taking prednisone at baseline. In the epoprostenol group, there was a nonsignificant trend toward a greater median distance walked at baseline, as well as a trend toward higher mean pulmonary vascular resistance at baseline.

Exercise Capacity

The distance walked in 6 minutes improved at week 12 in the epoprostenol group from a median of 270 m to 316 m and decreased in the conventional therapy group from a median of 240 m to 192 m. The difference in median distance walked (epoprostenol group minus conventional therapy group) at week 12 was 108 m (95% CI, 55.2 m to 180.0 m, Hodges–Lehmann estimate of the median difference) ($P < 0.001$, nonparametric analysis of covariance). Furthermore, the median change in distance walked by the two groups consistently diverged over time during the study (**Figure 2**). These differences, as analyzed by using parametric methods, were similar ($P < 0.001$).

Cardiopulmonary Hemodynamics

The changes in hemodynamic measures from baseline to week 12 are shown in **Table 3**. The epoprostenol-treated patients had significant improvement in mean pulmonary artery pressure, pulmonary vascular resistance, right atrial pressure, cardiac index, and mixed venous oxygen saturation

Table 3. Changes from Baseline in Cardiopulmonary Hemodynamic Measurements

Variable	Change from Baseline*		Difference between Groups (95% CI)†
	Epoprostenol Group	Conventional Therapy Group	
Pulmonary artery pressure, mm Hg	−5.03 ± 1.09	0.94 ± 1.10	−5.97 (−8.98 to −2.96)
Pulmonary vascular resistance, mm Hg/L per minute	−4.58 ± 0.76	0.92 ± 0.56	−5.50 (−7.33 to −3.67)
Right atrial pressure, *mm Hg*	−1.26 ± 0.82	1.20 ± 0.69	−2.46 (−4.54 to −0.39)
Cardiac index, *L/min per m²*	0.50 ± 0.08	−0.10 ± 0.08	0.60 (0.39 to 0.81)
Systemic arterial oxygen saturation, %	−0.33 ± 1.09	−0.31 ± 0.61	−0.02 (−2.45 to 2.42)
Mixed venous oxygen saturation, %	3.55 ± 1.42	−1.07 ± 1.24	4.62 (0.94 to 8.30)
Systemic arterial pressure, *mm Hg*	−8.26 ± 1.69	−0.63 ± 1.52	−7.63 (−12.07 to −3.2)
Heart rate, *beats/min*	3.74 ± 1.47	−0.90 ± 1.93	4.64 (−0.06 to 9.33)

* Data are expressed as the mean ± SE.
† A confidence interval that does not contain 0 implies statistical significance.

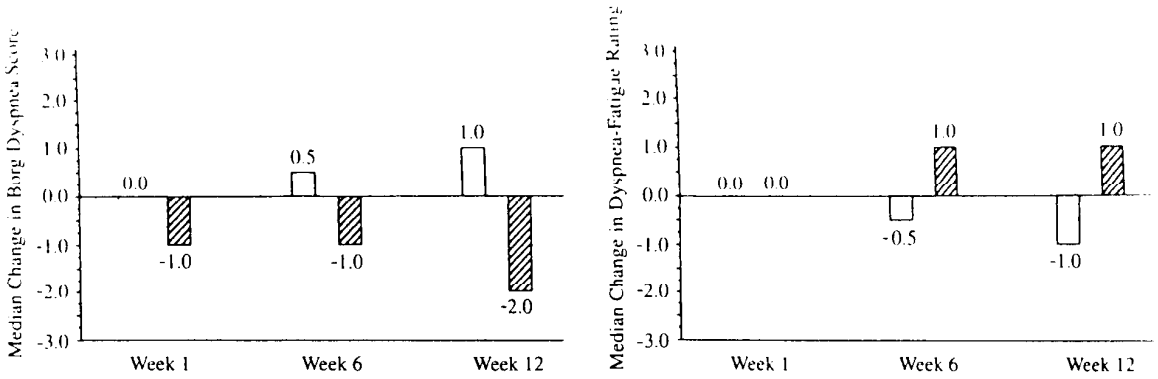

Figure 3. Median changes from baseline in Borg Dyspnea Score (*left*) and Dyspnea-Fatigue Rating (*right*) for the conventional therapy group (*white bars*) and the epoprostenol group (*striped bars*). A negative change from baseline (to a lower score) reflects an improvement in symptoms. Borg Dyspnea Scores improved (decreased) in the epoprostenol group and worsened (increased) in the conventional therapy group over 12 weeks. The Hodges–Lehmann estimate for the true treatment effect of epoprostenol compared with conventional therapy, based on the difference in change from baseline in the median Borg Dyspnea Score, was 1.0 (95% CI, 0.5 to 2.0) at week 1, 1.5 (CI, 1.0 to 2.5) at week 6, and 2.5 (CI, 1.5 to 3.5) at week 12. Dyspnea-Fatigue Ratings improved (increased) in the epoprostenol group and worsened (decreased) in the conventional therapy group over 12 weeks. The Hodges–Lehmann estimate for the true treatment effect of epoprostenol compared with conventional therapy, based on the difference in change from baseline in the median Dyspnea-Fatigue Rating, was 0.0 (CI, −1.0 to 0.0) at week 1, −2.0 (CI, −2.0 to −1.0) at week 6, and −2.0 (CI, −3.0 to −2.0) at week 12. Confidence intervals that do not contain 0 indicate statistical significance.

whereas these variables generally worsened in patients receiving conventional therapy. Systemic arterial pressure decreased in epoprostenol-treated patients.

Signs and Symptoms

At the end of 12 weeks, 21 patients (38%) treated with epoprostenol and no patients receiving conventional therapy showed improved NYHA functional class. Borg Dyspnea Scores and Dyspnea-Fatigue Ratings improved in the epoprostenol group and worsened in the control group (**Figure 3**).

A trend toward greater improvement in the Raynaud phenomenon severity score (a negative change) was seen in the epoprostenol group (mean change [±SE] from baseline at week 12, 1.69 ± 0.42 compared with −0.50 ± 0.54 in the conventional therapy group). When area under the curve analysis was done for severity of the Raynaud phenomenon over time based on a rank scale, values obtained were 43.1 ± 2.9 for the epoprostenol group and 52.3 ± 3.2 for the conventional therapy group ($P = 0.038$). Over the course of the study, a similar number of patients in each group had at least one new digital ulcer or ischemic demarcation event (10 of 52 patients [19%] in the epoprostenol group and 11 of 52 patients [20%] in the conventional therapy group). A total of 36 new digital ulcers occurred in the epoprostenol group and 72 occurred in the conventional therapy group.

Table 4. Incidence of Selected Adverse Events

Adverse Event	Epoprostenol Group	Conventional Therapy Group
	n (%)	
Disease-related		
Syncope	4 (7)	11 (20)
Pallor	18 (32)	29 (53)
Ascites	13 (23)	18 (33)
Epoprostenol-related		
Anorexia	37 (66)	26 (47)
Nausea	23 (41)	9 (16)
Diarrhea	28 (50)	3 (5)
Jaw pain	42 (75)	0 (0)
Depression	7 (13)	2 (4)
Drug delivery system–related		
Sepsis	2 (4)	–
Cellulitis	2 (4)	–
Hemorrhage	2 (4)	–
Pneumothorax	2 (4)	–

Safety and Survival

During the 12-week study period, 5 patients in the conventional therapy group and 4 in the epoprostenol group died (*P* value not significant). Causes of death in the conventional therapy group were respiratory failure (2 patients), progressive right-heart failure (1 patient), acute pulmonary edema (1 patient), and arrhythmia (1 patient). Causes of death in the epoprostenol group were progressive right-heart failure (1 patient), myocardial infarction (1 patient), septic shock (1 patient), and sudden death (1 patient). Patients who died tended to have a longer median duration of the scleroderma spectrum of disease than survivors in both the epoprostenol (90 and 60 months) and conventional therapy (168 and 40 months) groups. In contrast, patients who died and those who survived had the same duration of pulmonary hypertension (7 and 8 months.).

Selected adverse events attributed to the underlying disease, epoprostenol, or the drug delivery system are shown in **Table 4**. Disease-related or cardiovascular events, including syncope and pallor, occurred less commonly in patients receiving

epoprostenol. Although events involving the digestive system were common in both treatment groups, anorexia, nausea, and diarrhea were more common in epoprostenol-treated patients. Jaw pain occurred commonly in the epoprostenol group. The drug delivery system, including the central venous catheter and the infusion pump, was associated with eight catheter-related adverse events, including sepsis, cellulitis, hemorrhage, and pneumothorax (**Table 4**). No clinically significant changes in hematologic or biochemical variables were seen.

Discussion

Pulmonary hypertension in patients with the scleroderma spectrum of disease is associated with a poor prognosis, and no therapy has been proven effective. Moreover, many patients with scleroderma are not candidates for lung transplantation because of the systemic nature of the disease. We documented improvement in exercise capacity, cardiopulmonary hemodynamics, and indices of dyspnea in patients with pulmonary hypertension secondary to the scleroderma spectrum of disease who received epoprostenol plus conventional therapy rather than conventional therapy alone. As expected, exercise capacity and hemodynamic function tended to deteriorate or remained unchanged with conventional therapy. Trends toward greater improvement in the severity of the Raynaud phenomenon and fewer new digital ulcers were observed in the epoprostenol group.

Continuous infusion of epoprostenol is associated with dose-related side effects, including jaw pain, headache, nausea, anorexia, and diarrhea, and with complications related to the drug delivery system, such as cellulitis, sepsis, hemorrhage, and pneumothorax (6). Patients can tolerate many of the side effects well, and intolerable side effects often respond to a slight reduction in dose. Serious or life-threatening drug-related complications are rare. Patients with suspected pulmonary veno-occlusive disease should be approached cautiously because epoprostenol may precipitate acute and potentially fatal pulmonary edema (4, 66).

Our study differs from a previous study of continuously infused epoprostenol in patients with primary pulmonary hypertension (6) in several ways. In our study, the severity of pulmonary hypertension at baseline was defined hemodynamically as opposed to by NYHA class. In contrast to the previous study (6), our patients did not undergo hemodynamically monitored short-term dose-ranging of epoprostenol, nor were they required to have had unsuccessful previous conventional vasodilator therapy. Hemodynamically monitored short-term dose ranging was performed in the previous study because approximately 25% of patients with primary pulmonary hypertension will respond to an acute vasodilator challenge, and these patients may be treated effectively with conventional vasodilators (67–74). Furthermore, short-term dose-ranging of epoprostenol with hemodynamic monitoring is not required for the safe institution of long-term epoprostenol therapy. Despite these differences in patient population and study design, the physiologic results of our study were similar to those of the previous study (6). In both studies, exercise capacity, cardiopulmonary hemodynamics, and NYHA functional class significantly improved with epoprostenol therapy.

Unlike the earlier study of epoprostenol in primary pulmonary hypertension (6), we did not find a survival benefit. In designing our study, a power analysis indicated that enrollment of least 235 patients would be needed to give an 80% likelihood of detecting a survival benefit. A study of such size was not feasible. Additional possible reasons for the lack of a survival difference between treatment groups in the current study include the greater complexity of illness and multiorgan involvement in scleroderma and perhaps differences in the structural component of pulmonary vascular involvement (75–77). The finding that a greater duration of scleroderma was associated with poorer survival in both the epoprostenol and control groups supports the former possibility.

As in the earlier study of continuous intravenous epoprostenol therapy in primary pulmonary hypertension (6), a limitation of our study was that it was not a double-blind, placebo-controlled trial. Because of the known incidence of sepsis caused by indwelling central venous catheters (6, 78, 79), a placebo-controlled study was considered unethical. Furthermore, unique and predictable symptoms known to occur during long-term epoprostenol treatment (such as flushing, jaw pain, and diarrhea) prevented blinding of physicians and patients. Another limitation of our study is the lack of formal quality-of-life instruments and cost data, although the assessment of exercise capacity, Borg Dyspnea Score, Dyspnea-Fatigue Rating, NYHA functional class, and indices of the severity of the Raynaud phenomenon provides some information on quality of life.

We conclude that continuous intravenous infusion of epoprostenol plus conventional therapy in patients with pulmonary hypertension secondary to the scleroderma spectrum of disease improved exercise capacity, cardiopulmonary hemodynamics, NYHA functional class, and indices of dyspnea compared with conventional therapy alone. This is the first randomized trial of therapy for secondary pulmonary hypertension. Although the results of this study apply specifically to pulmonary hypertension in the scleroderma spectrum of disease, the potential ther-

apeutic implications for a broader group of patients warrant further consideration.

Appendix

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EDITORIAL

Epoprostenol (Prostacyclin) and Pulmonary Hypertension

Pulmonary hypertension is a prevalent disorder, and the list of its causes is long and varied. Included in the list, which is densely populated by so-called secondary types of pulmonary hypertension, is the category of unexplained (primary) pulmonary hypertension, presumably the final common pathway for multiple unidentified causes. For those concerned with the pathogenesis of the more common and diverse pulmonary hypertensive disorders that make up the category of secondary pulmonary hypertension, interest in primary pulmonary hypertension is high because it represents a model of "pure" intrinsic pulmonary vascular disease, uncomplicated by concomitant disease of the heart or lungs. Those concerned with therapy continue to direct their attention at relief of pulmonary vasoconstriction, which seems to be involved in the pathogenesis of primary pulmonary hypertension (1).

Before epoprostenol (prostacyclin) became available for clinical use, primary pulmonary hypertension was a calamitous disorder, destined to pursue a relentlessly downhill course that ended in right ventricular failure within 2 to 3 years. All sorts of systemic vasodilators were tried as pulmonary vasodilators, with largely inconsistent or futile results. The advent of prostacyclin introduced the most potent vasodilator known; other useful attributes of this agent are antiplatelet aggregation and adhesion inhibition of smooth-muscle proliferation. It marked the end of inevitability of early death and the beginning of a brighter outlook for quality of life in primary pulmonary hypertension.

The first applications of prostacyclin were diagnostic. They led to the recognition of prostacyclin as the "gold standard" for testing the ability of the hypertensive pulmonary circulation to undergo vasodilation (2). The pulmonary hypertension centers that were established by the National Heart, Lung, and Blood Institute as part of the National Registry on Primary Pulmonary Hypertension played an important role in the recruitment of sufficient numbers of patients with primary pulmonary hypertension. The collective experience indicated that prostacyclin elicited pulmonary vasodilation in only about one third of patients with primary pulmonary hypertension. Although these results were somewhat disappointing, identification of such responders was subsequently turned to an advantage by the demonstration that disease in responders could be managed successfully with oral calcium-channel blockers instead of more demanding routes, such as continuous intravenous infusion of prostacyclin (3, 4).

The role of prostacyclin in the management of primary pulmonary hypertension began to switch from diagnosis to treatment when continuous intravenous administration of prostacyclin was shown to serve as a life-saving bridge to lung transplantation (5). An even greater role followed the disclosure that patients with primary pulmonary hypertension who did not respond to acute testing with prostacyclin would improve hemodynamically and clinically with continuous intravenous administration of prostacyclin (6, 7). How continuous administration of prostacyclin decreased pulmonary vascular resistance was, and still is, enigmatic. Because the decrease in pulmonary vascular resistance could not readily be ascribed to vasodilation, consensus emerged that structural changes, so-called remodeling, were involved. How prostacyclin managed this remodeling is still speculative.

A logical extension of this gratifying experience with prostacyclin in primary pulmonary hypertension was to apply the same treatment to patients with secondary pulmonary hypertension in which the pulmonary vascular lesions are histologically indistinguishable from those of primary pulmonary hypertension (8). The scleroderma spectrum of disease seemed to fit the bill for several reasons. First, pulmonary hypertension is a common complication, and often a cause of death, in diffuse scleroderma, particularly the CREST syndrome (calcinosis cutis, the Raynaud phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia) (9). Second, the pulmonary vascular lesions of scleroderma resemble those of primary pulmonary hypertension. Third, recent reports have suggested that the clinical and hemodynamic improvements produced by prostacyclin in primary pulmonary hypertension can be replicated in pulmonary hypertension resulting from the scleroderma spectrum of disease (4, 10–12). Finally, the Raynaud phenomenon, which occurs in primary pulmonary hypertension as well as in

scleroderma, has been reported to improve with prostacyclin or its analogues (13).

Against this background, Badesch and colleagues (9) undertook a 12-week unblinded, randomized, multicenter, controlled trial of intravenous prostacyclin for moderate to severe pulmonary hypertension in patients with scleroderma. They found that prostacyclin relieved symptoms and improved both exercise capacity and cardiopulmonary hemodynamics. In contrast, controls who received conventional therapy deteriorated. The reason why survival was the same in both the test and control groups requires future study in a larger sample. In addition, the study did not address the question of whether acute testing for pulmonary vasoresponsiveness would have identified a subgroup of responders that could have been treated successfully with a less demanding vasodilator program, such as calcium-channel blockers taken orally (4).

Unfortunately, despite the favorable outcomes, continuous intravenous prostacyclin is far from ideal as treatment of pulmonary hypertension: The agent is available in only limited supply; it is very costly; and optimal management requires that the intravenous therapy with prostacyclin be started in specialized centers that have become familiar with the technique, equipment, and dose ranging, although ongoing care can be delivered by physicians briefed by and in continuing contact with the centers. Moreover, continuous intravenous administration of prostacyclin exacts a high, albeit usually tolerable, price in discomfort and disability. Jaw pain, nausea, and anorexia are common, and the patient is continually under the hanging sword of complications from prolonged catheterization and breakdowns in the delivery system. Moreover, mistaking pulmonary veno-occlusive disease for the more usual precapillary type of primary pulmonary hypertension creates the risk that prostacyclin will precipitate life-threatening pulmonary edema (14).

The salutary effects of continuous intravenous vasodilator therapy have encouraged trials of other agents delivered by different routes. Agents currently under study include antivasoconstrictors, such as antiendothelins, and vasodilators, such as analogues of prostacyclin, adenosine, and nitric oxide. UT-15, an analogue of prostacyclin, is being administered by subcutaneous injection. Inhalation is an alternate route that has been tried for prostacyclin and for iloprost, its more stable and accessible analogue, as well as for nitric oxide. Olschewski and associates put this approach to the test (15). Extending the results of their previous studies of patients with primary or secondary pulmonary hypertension, researchers at six centers in Germany undertook "rescue attempts" with inhaled iloprost or nitric oxide in 19 patients with severe pulmonary hypertension who were in or were verging on right-heart failure. At 3 months, 12 of the 19 patients had clinical and hemodynamic improvement; 7 could continue using this regimen for 1 year or longer. Iloprost seemed to work better than nitric oxide.

This uncontrolled trial leaves several unanswered questions that stem from the relatively small number of patients, the different causes of the pulmonary hypertension, and uncertainties about the severity of the pulmonary hypertension in individual patients. Most desirable but difficult to achieve would be a controlled clinical trial to compare the effectiveness of inhaled prostacyclin with that of continuous intravenous prostacyclin over months to years. Although the inhalation route has attractive features, the practicality of a standard regimen for delivery of inhalants, such as iloprost or nitric oxide, to outpatients for years remains to be shown. Moreover, whether agents other than prostacyclin, such as nitric oxide, can accomplish long-term remodeling is unknown.

Both studies in this issue can be viewed as pioneering efforts in different stages of evolution. Badesch and colleagues' study (9) is the first randomized trial of treatment for secondary pulmonary hypertension. The article by Olschewski and associates (15) is a harbinger of new trials in the search for novel routes and agents that will improve on the success of continuous intravenous infusion of prostacyclin (16).

Until now, almost all of the advances in the management of primary pulmonary hypertension and intrinsic pulmonary vascular pathology have been directed at relieving pulmonary vasoconstriction. The use of prostacyclin and other vasodilators is now being extended beyond primary pulmonary hypertension and the scleroderma spectrum of pulmonary hypertension to subsets of secondary pulmonary hypertension, such as congenital heart disease, in which the pulmonary vascular histopathology is similar (17). On the immediate list of targets for trial with pulmonary vasodilators are causes of pulmonary hypertension such as HIV, anorectic agents, and familial pulmonary hypertension. In the meantime, the feasibility and effectiveness of long-term therapy with inhalants continue to be evaluated (18, 19).

Preoccupation with vasodilators in managing pulmonary hypertension should not obscure the fact that vasodilation seems to be only one effect of prostacyclin. The purported remodeling induced by continuous infusion of prostacyclin has raised the possibility of medically arresting or reversing the factors involved in proliferative and occlusive pulmonary vascular disease (20). Whether agents other than prostacyclin share this potential is under investigation.

In addition to the possibility of reversing the proliferative vascular changes and remodeling the pulmonary hypertensive circulation, other bright prospects for dealing with pulmonary hypertension seem to be in the offing. High on the list is the likelihood that the genetic bases for primary pulmonary hypertension will soon be defined, along with a better understanding of inherited predisposition to pulmonary hypertension. Should these promises live up to expectations, the treatment of pulmonary hypertension will shift from the current empirical management of abnormal hemodynamics and clinical manifestations to the prevention and treatment of pulmonary hypertensive disorders on the basis of a firm grasp of etiology, individual susceptibility, and pathogenetic mechanisms.

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Reference

9. Guyatt, G.H. et al The 6-minute Walk: A new measure of exercise capacity in patients with chronic heart failure. Can. Med. Assoc. J., Vol. 132, 1985, 9190923.

The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure

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Cycle and treadmill exercise tests are unsuitable for elderly, frail and severely limited patients with heart failure and may not reflect capacity to undertake day-to-day activities. Walking tests have proved useful as measures of outcome for patients with chronic lung disease. To investigate the potential value of the 6-minute walk as an objective measure of exercise capacity in patients with chronic heart failure, the test was administered six times over 12 weeks to 18 patients with chronic heart failure and 25 with chronic lung disease. The subjects also underwent cycle ergometer testing, and their functional status was evaluated by means of conventional measures. The walking test proved highly acceptable to the patients, and stable, reproducible results were achieved after the first two walks. The results correlated with the conventional measures of functional status and exercise capacity. The authors conclude that the 6-minute walk is a useful measure of functional exercise capacity and a suitable measure of outcome for clinical trials in patients with chronic heart failure.

La bicyclette ergométrique et le tapis roulant sont mal adaptés à l'examen du malade âgé et affaibli souffrant d'insuffisance cardiaque et ne renseignent peut-être pas sur sa capacité dans les activités de la vie quotidienne. Comme les épreuves à la marche ont su éclairer le pronostic dans l'insuffisance respiratoire chronique, on a voulu voir si la marche de 6 minutes se prêterait à l'étude objective de la tolérance à l'exercice dans l'insuffisance cardiaque chronique. L'épreuve est faite six fois en 12 semaines chez 18 malades atteints d'insuffisance cardiaque chronique et 25 atteints d'insuffisance pulmonaire chronique. On pratique aussi chez tous les sujets une ergométrie à la bicyclette et un bilan fonctionnel par les méthodes classiques. L'épreuve à la marche s'avère hautement satisfaisante du point de vue des malades. À partir de la troisième marche on obtient des résultats fiables et reproductibles qui sont en corrélation avec ceux de l'étude fonctionnelle et de l'ergométrie. On conclut que chez le malade souffrant d'insuffisance cardiaque chronique, la marche de 6 minutes est utile pour la mesure de la tolérance à l'exercice et pourrait servir de barème dans l'analyse des essais cliniques.

Over the last decade the advent of vasodilator therapy and, more recently, the exploration of new inotropic agents have led to a reawakened interest in the treatment of chronic heart failure. Problems have arisen in measuring the benefit of these drugs for patients with heart failure: the three major approaches — measurement of functional status, measurement of hemodynamic variables and measurement of exercise capacity — all have important limitations. The functional classification of the New York Heart Association (NYHA) is imprecise[1] and subjective and provides no information about the mechanism of benefit. While objective and reproducible, the results of hemodynamic studies bear little or no relation to measures of functional status or of exercise capacity.[2-5] Conventional exercise testing can be difficult in patients who are extremely limited by severe cardiac dysfunction. Also, as vasodilators and inotropes may improve resting and exercise hemodynamics without increasing maximum exercise power output,[6-8] a submaximal exercise test may be a better method of assessing the benefit of interventions in patients with heart failure.[9]

Similar problems face investigators examining treatments for patients with chronic lung disease. As a possible solution to these difficulties, McGavin and colleagues[10] introduced the 12-minute walking test, in which patients are asked to walk as far as they can during a 12-minute period. Walking tests have since proved very useful and have been used to test the

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efficacy of a variety of physiologic and pharmacologic treatments for patients with chronic lung disease.

Walking tests are simple, inexpensive and safe. They clearly correspond more closely to the demands of everyday activities than does cycle ergometer exercise testing. The same is true, although to a lesser extent, of treadmill exercise testing, which may be intimidating to the frail, elderly or severely disabled and in which the rate of exercise is not under the patient's control. In addition, evidence to date suggests that results of the walking test are highly reproducible[11,12] and show moderate to strong correlations with other measures of exercise capacity and with self-reported measures of functional status.[10,11,13,14] Finally, a positive therapeutic effect was found in 10 of 13 studies in which the walking test was used as a measure of outcome in patients with chronic lung disease;[15-24] in two of the studies statistically significant improvement in exercise capacity was found with the walking test but not with concurrently administered conventional exercise tests.[15,16]

Although most investigators have used a 12-minute walk, Butland and coworkers[12] recently demonstrated that equivalent results can be obtained with a 6-minute walk, which has the advantages of being efficient and less stressful for the patient and corresponding more closely to the usual day-to-day activity of moderately or severely limited patients.

Walking tests may be as useful a measure of exercise capacity in patients with chronic heart failure as they have proven to be in those with chronic lung disease. To investigate the potential value of the 6-minute walk as an objective measure of exercise capacity in patients with chronic heart failure, we administered the walk six times to a group of patients whose primary problem was congestive heart failure and to another group whose disability was primarily due to chronic lung disease. Our objectives were to determine the reproducibility of test results in the cardiac and respiratory groups, the pattern of changes in test scores over time in the two groups, the response in the two groups to encouragement during testing, and the relation between conventional exercise testing and measures of functional status on the one hand and walking-test scores on the other in patients with heart failure. The implications of our findings for respiratory patients have been discussed elsewhere.[25]

Methods

We recruited patients who experienced dyspnea or fatigue while performing activities of daily living. Respiratory patients attended a regional referral centre for patients with pulmonary problems and had a best recorded forced expiratory volume in 1 second (FEV_1) less than 0.7 of the predicted value. Patients with heart failure were referred by local cardiologists and had impaired left ventricular function, as demonstrated by angiography, radionuclide scanning or echocardiography.

Exclusion criteria for both groups were as follows:

- Limitation of activity because of factors other than fatigue or exertional dyspnea, such as arthritis, claudication in the legs or angina.
- Psychiatric disease preventing reliable performance of the walking test.
- Admission to hospital in the 2 months before entry into the study.
- Previous experience with walking tests.

Each patient was tested six times, with 2-week intervals between the tests. Patients were stratified into the cardiac or respiratory group and then randomly assigned to receive or not receive encouragement. All the patients were initially tested without encouragement, and then, according to the randomization schedule, encouragement was consistently either given or not given during the five subsequent walks.

The walking tests were conducted in an enclosed corridor on a course 33 m long. The patients were instructed to walk from end to end, covering as much ground as they could during the allotted time. For the unencouraged group the supervisor sat in a chair at one end of the course, avoiding eye contact with the patient and remaining silent. The supervisor called out "Stop" when 6 minutes had elapsed, and the distance walked was determined. For the encouraged group the supervisor ensured that at 30-second intervals she was facing the subject and then delivered one of a predetermined set of encouraging phrases, such as "You're doing well" or "Keep up the good work". At the end of the test she called out "Stop", and the distance walked was recorded.

Each participant underwent a maximal exercise test using a bicycle ergometer according to the protocol of Jones.[26] The subjects spent 1 minute at each work load beginning at 100 kpm/min and increasing by increments of 100 kpm/min until they were too exhausted to continue.

One of us (M.J.S.), who was blinded to the results of all the other tests, interviewed and examined the patients and evaluated their functional status according to the NYHA criteria. At the time of each walking test the Specific Activity Scale, which has been reported to be a more reliable and valid measure of functional status in cardiac patients than the NYHA classification,[1] was administered to each patient by the test supervisor.

Statistical analysis

The results of the study were assessed by means of an analysis of variance, with the distance walked during the first test as a covariate. Three factors were examined: time (test repetition), encouragement and diagnostic group (respiratory or cardiac). Both main effects and interactions were examined. Because Mungall and Hainsworth[11] found improvement in walking-test scores over the first three of six 12-minute walks, we compared the scores on the first two walks with those on the last four.

To assess the variability in walking-test performance over time, the within-person standard deviation for the last four walks was calculated for both groups.

To examine the relation between walking-test scores and the other measures, Spearman rank correlation coefficients between the walking-test scores and the results of cycle ergometer testing were calculated.

mean score on the last four walks was used for the correlation, and the results were pooled across the encouraged and unencouraged groups.

Results

Of the 57 patients entered in the study 43 (34 men and 9 women) completed the six visits (Fig. 1); their mean age was 64.7 ± 8.3 years. There were 25 respiratory patients and 18 cardiac patients: 23 were in the encouraged group and 20 in the unencouraged group. Of the 14 dropouts 9 were cardiac patients and 5 respiratory patients; 7 had been assigned to the encouraged group and 7 to the unencouraged group. Seven dropped out for reasons unrelated to the study: death, fractured hip, exacerbation of underlying disease, move away from the area, development of concurrent illness or family problems. One patient with heart failure experienced increasing symptoms after his first two walking tests and declined to continue. The remaining six patients expressed dissatisfaction with the study (e.g., "I felt ill after the walking tests"; "The walks didn't seem to be beneficial"; "A doctor wasn't present") and dropped out. Most dropouts occurred after the first walking test (Fig. 1).

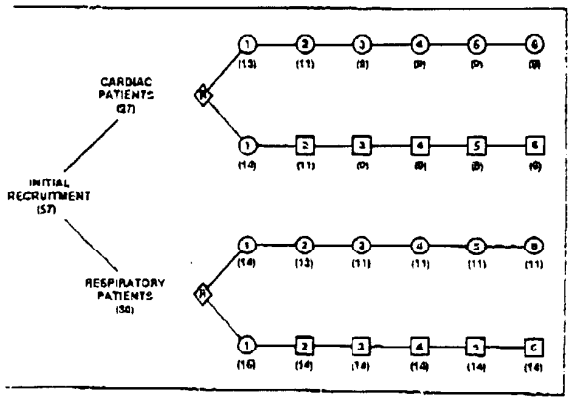

Fig. 1—Study design for 6-minute walk. ○ = without encouragement; □ = with encouragement; numerals within symbols indicate visit number; numerals in parenthesis indicate number of patients; R = randomization.

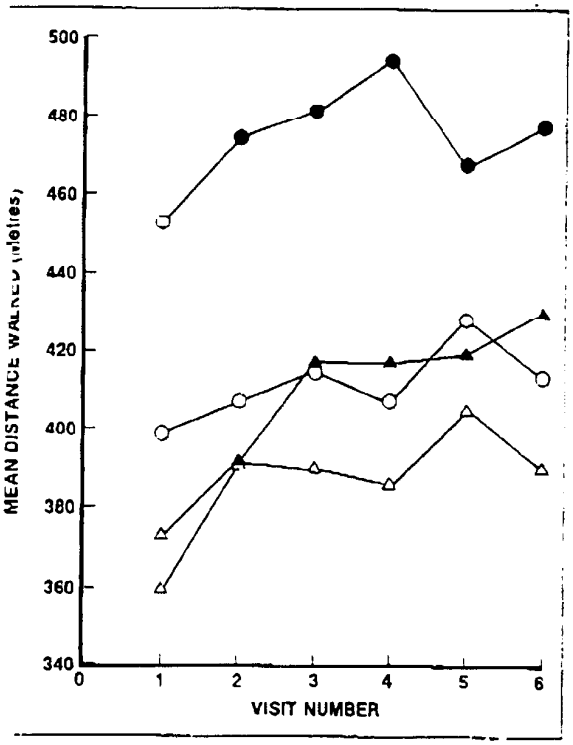

Fig. 2—Mean distance walked by 18 cardiac and 25 respiratory patients during six walking tests. ● = encouraged cardiac group; ○ = unencouraged cardiac group; ▲ = encouraged respiratory group; △ = unencouraged respiratory group.

The 25 respiratory patients had a mean FEV_1 of 0.97 ± 0.25 L and a mean vital capacity of 2.4 ± 0.87 L. Of the 18 cardiac patients 5 were in NYHA class II, 12 were in class III and 1 was in class IV. All but two had a cardiothoracic ratio greater than 0.5, as determined by posteroanterior chest roentgenography. All were taking both digoxin and one or more diuretics, and 12 were taking vasodilators (prazosin, hydralazine, captopril or nitrates). Eight of the participants met the inclusion criteria for both diagnostic groups.

Encouragement improved walking-test performance ($p < 0.02$), and the respiratory patients improved more over time than did the cardiac group, irrespective of encouragement ($p < 0.05$) (Fig. 2). There was no interaction between diagnostic group and encouragement, which suggests that encouragement had a similar effect on the two groups.

Although the cardiac patients walked farther than did the respiratory patients, this difference did not reach statistical significance ($p = 0.178$) because of the small sample size and the large between-person variability. The large difference in baseline scores between encouraged and unencouraged cardiac patients was a chance phenomenon.

Comparison of the results of the first two walks with those of the last four showed that the subjects walked farther during the last four walks ($p < 0.001$) (Fig. 2). The scores plateaued during the last four walks.

The variability of test results was comparable for both the cardiac and the respiratory patients irrespective of encouragement, and the within-person standard deviation was in each case less than 6% of the mean score. That is, the subjects' walking-test scores were within 6% of their mean score 65% of the time and within 12% of their mean score 95% of the time. This compares favourably with the results of most clinical and laboratory tests; for example, the variability of results of spirometry in patients with chronic airflow limitation[11] was approximately twice the variability we found in the walking test.

The correlations between the mean walking-test score and the results of cycle ergometer testing and functional classification were similar in the cardiac and respiratory groups, and the magnitude of the correlations was low to moderate (Table I). Sicker patients received higher scores on the NYHA classification and the Specific Activity Scale and walked shorter distances; thus, the correlations between walking-test scores and results of functional classification were negative.

Discussion

In accordance with the results of previous work,[11,12] we found that both the cardiac and the respiratory group showed improvement in walking-test scores up to the third walk, and consistent results were obtained thereafter. The high precision seen in both groups following the first two walks (Table I) suggests that in clinical trials in patients with heart failure in which the 6-minute walk is used as a measure of outcome, it will be possible to detect small treatment effects with feasible sample sizes. For example, with conventional specifications for both power and statistical significance and an independent groups design, one would need only 13 subjects per group to detect an improvement in score of 25 m (which is about 6% of the mean baseline score and less than the effect of encouragement in our study).

Since encouragement had a substantial impact on walking-test scores ($p < 0.02$) that was similar in both the cardiac and the respiratory patients, administration of the test should be rigorously standardized in both patients with chronic heart failure and those with chronic lung disease.

The correlations between walking-test scores and conventional measures were low to moderate in magnitude, statistically significant and similar in the cardiac and respiratory patients (Table I). The low correlation with the results of cycle ergometer testing suggests that the walking test measures something different: since walking is a regular daily activity, the walking test may measure a patient's ability to undertake the physically demanding activities of day-to-day life, as opposed to laboratory exercise capacity. If this were so, one might have expected higher correlations with the measures of functional status. However, the limitations of the functional classifications (including limited reliability and the fact that both classifications have only four categories) may have attenuated the correlations. In other studies in respiratory patients walking-test scores correlated well with other measures of functional status.[13,14] This issue needs further exploration in patients with heart failure.

In summary, in the patients with chronic heart failure the 6-minute walk was both safe and highly acceptable to the patients and produced stable results after the first two walks. The results were reproducible and correlated with conventional measures of functional status and exercise capacity. The walking test appears promising as a simple measure of functional exercise capacity for clinical trials in patients with chronic heart failure.

Table I—Correlations between walking-test scores and results of functional classification and cycle ergometer testing in cardiac and respiratory patients

Test	Diagnostic group: Cardiac ($n = 18$)	Respiratory ($n = 25$)	Total ($n = 43$)	p value ($n = 18$)*
New York Heart Association functional classification	−0.45			0.058
Specific Activity Scale†	−0.37	−0.52	−0.47	0.001
Cycle ergometer	0.42	0.57	0.58	< 0.001

*Pairwise analysis.

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ANNOUNCEMENT OF MEETINGS

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Date
Title
Place and city
Contact person and telephone number

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June

June 6–13, 1985

Canadian Anaesthetists' Society annual meeting
Hilton Harbour Castle Hotel, Toronto
Mr. Frank A. Teepell, Executive director, Canadian Anaesthetists' Society, 94 Cumberland St., Ste. 901, Toronto, Ont. M5R 1A3; (416) 923-1449

August

Aug. 24–27, 1985

International Meeting on Immunogenetics of Endocrine Disorders
St. John's, Nfld.
Dr. Nadir R. Farid, Program chairman, International Meeting on Immunogenetics, Health Sciences Centre, Memorial University of Newfoundland, St. John's, Nfld. A1B 3V6; (709) 737-6300

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10. McLaughlin, V. et al. Continuous subcutaneous infusion of Remodulin, a prostacyclin analogue in patients with pulmonary arterial hypertension: Long-term Outcome. (Abstract) HFSA 5th Annual Scientific Meeting, September, 2001.

Presenting/Contact Author: Executive VP Shelmer D Blackburn **Category:** Clinical trials

HFSA 5th Annual Scientific Meeting

Abstract Number: 441
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Category: 7 Clinical trials
Format Type: No Preference **Continuous Subcutaneous Infusion of Remodulin ™, a Prostacyclin Analogue, in Patients with Pulmonary Arteri al Hypertension: Long-Term Outcome** Vallerie V. McLaughlin [1], Olivier Sitbon [2], and Shelmer D. Blackburn, Jr. [3] for the Remodulin Study Group, [1], Rush-Presbyterian-St. Lukes Medical Center, Chicago, IL; [2], Hopital Antoine-Beclere, Clamart, France; and [3], United Therapeutics Corporation, Research Triangle Park, NC.

631 patients (mean age 45±0.6 years) with pulmonary arterial hypertension (PAH) were enrolled in this ongoing, international, open-label study to investigate the long-term benefits of Remodulin, a prostacyclin analogued administered by continuous, subcutaneous delivery. Etiology of PAH included primary pulmonary hypertension (59%), connective tissue disease (19%) and congenital heart disease (23%).

Objectives - To determine the safety of long-term Remodulin use; however, exercise capacity (utilizing the six minute walk test) was also captured in those patients who had the test performed as part of their routine clinical follow-up.

Methods - Patients who were previously enrolled in earlier controlled trials of Remodulin and continued therapy, and newly diagnosed patients meeting entry criteria were enrolled. Dosing and adverse experiences were assessed throughout the study.

Exposure - Six months - 426 (68%) patients; 12 months - 224 (35%) patients; 18 months - 47 (7%) patients; 24 months - 12 (2%) patients.

Results - Six Minute Walk Test results and long-term dosing are shown below:

Month	No. Patients (%enrolled)	Dose (ng/kg/min)	Exercise (meters)
Baseline	406 (64)	NA	334±4.6
6	156 (38)	16±0.7	+34±6
9	112 (34)	19±1.3	+34±8
12	102 (37)	25±1.7	+33±7
15	63 (35)	24±2.1	+37±12
18	46 (43)	31±3.1	+46±13
21	15 (38)	38±7.1	+55±17

The most common drug related adverse events included infusion site pain (83%), infusion site reaction (76%), diarrhea (27%), nausea (20), headache (18), infusion site bleed/bruise (15), jaw pain (15) and other pain (12).

Conclusions - Exercise is improved with long-term administration of Remodulin; this effect appears to be dose related, with chronic doses increasing over time. Remodulin is tolerated in most patients; reasons for discontinuations from study included adverse events (15%, mostly infusion site pain), clincial deterioration (6%) and death (6%). Infusion site side effects occurred more frequently than systemic, well known prostaglandin-type side effects, but were generally tolerated and managed with various therapies.